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From:	EMCDDA
To:	Delegations
Subject:	Risk assessment report on a new psychoactive substance: 2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl)

Following the Council's request to conduct a Risk Assessment on a new psychoactive substance: 2-methoxy-N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl), the EMCDDA hereby presents the above-mentioned Risk Assessment Report drawn up by its Scientific Committee pursuant to Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances.

ANNEX

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

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

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 2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (commonly known as methoxyacetylfentanyl). 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 methoxyacetylfentanyl, 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]).

([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.

Methoxyacetylfentanyl was formally notified on 9 December 2016 by the EMCDDA on behalf of Slovenia, in accordance with Article 4 of the Council Decision. The notification related to the collected sample of 5 grams of brown powder that was test-purchased as part of the EU co-funded RESPONSE project. Following an assessment of the available information on methoxyacetylfentanyl, and in accordance with Article 5 of the Council Decision, on 19 December 2017, the EMCDDA and Europol submitted a *Joint Report* on methoxyacetylfentanyl ([6]) to the 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl, 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 2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl) (Annex 1);
- EMCDDA–Europol Joint Report on a new psychoactive substance: 2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl) ([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]).

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

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 methoxyacetylfentanyl. 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 methoxyacetylfentanyl that was invented in 1985.

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.

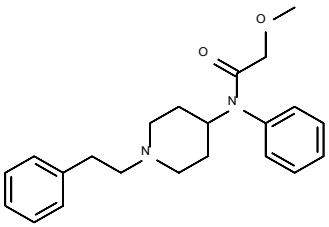
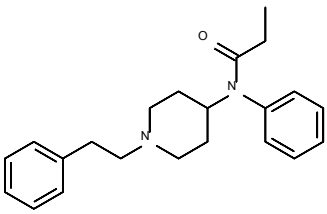
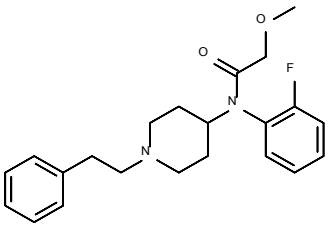
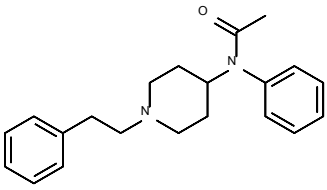
3. Physical, chemical and pharmacological description

Physical and chemical description

2-Methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl) 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. Methoxyacetylfentanyl is also structurally related to ocfentanil and to acetylfentanyl (Figure 1).

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

Figure 1. Molecular structure of methoxyacetylfentanyl. Information on fentanyl, ocfentanil, and acetylfentanyl is provided for comparison.

	
methoxyacetylfentanyl	fentanyl
	
ocfentanil	acetylfentanyl

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

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

Methoxyacetylfentanyl is not expected to give a positive response to immunoassays developed for morphine-type opioids. At least three commercially available immunoassays for fentanyl appear to detect methoxyacetylfentanyl. In addition, LSD immunoassays may detect methoxyacetylfentanyl.

As methoxyacetylfentanyl 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

Methoxyacetylfentanyl has been detected in powders and liquids, and, to a lesser extent, in tablets. Some of the liquids were detected in nasal sprays and in syringes.

Pharmacological description

Pharmacologically, methoxyacetylfentanyl is an opioid receptor agonist.

Currently available data on the pharmacodynamics of methoxyacetylfentanyl are limited to studies investigating its binding and functional activity at opioid receptors *in vitro*, and its anti-nociceptive properties in mice. The *in vitro* data shows that methoxyacetylfentanyl is a highly selective μ-opioid receptor agonist and that it is less potent than morphine and fentanyl. Data from studies in mice examining the anti-nociceptive properties of methoxyacetylfentanyl shows that the substance reduces the response to experimentally induced pain with a similar potency to other controlled fentanils.

Due to its lipophilicity, methoxyacetylfentanyl should be rapidly absorbed and readily cross the blood-brain barrier. A recent study indicates that the metabolic pathway of methoxyacetylfentanyl shares some similarities with other fentanils. Consequently, 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 methoxyacetylfentanyl 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, methoxyacetylfentanyl 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

Methoxyacetylfentanyl 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 methoxyacetylfentanyl is used for other legitimate purposes.

There are no reported uses of methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl detected on the drug market within the European Union.

The synthesis of methoxyacetylfentanyl, using *N*-phenethyl-4-piperidone (NPP), and aniline as precursors to yield *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP), which is then reacted with methoxyacetyl chloride, has been described in the literature in a patent from 1985. Both NPP and 4-ANPP were scheduled in 2017 ([7]).

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 methoxyacetylfentanyl. 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.

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.

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

Methoxyacetylfentanyl 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.

5. Health risks

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of methoxyacetylfentanyl, 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 methoxyacetylfentanyl. 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 methoxyacetylfentanyl 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.

Methoxyacetylfentanyl appears to be used in combination with other drugs (intentionally or unintentionally) as part of polydrug use.

While no specific examples are available, it is reasonable to assume, that, similar to other fentanils, methoxyacetylfentanyl may be supplied through the illicit opioid market.

Acute toxicity

The acute toxicity of methoxyacetylfentanyl has been assessed in mice in one study which suggests that it is similar to that of fentanyl. No studies were identified that have investigated the acute effects of methoxyacetylfentanyl in humans.

Although the pharmacology and toxicology of methoxyacetylfentanyl largely remains 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: 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 methoxyacetylfentanyl, 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl. 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 benzodiazepine and analgesic 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

Two acute intoxications with confirmed exposure to methoxyacetylfentanyl were reported to the EMCDDA by the Czech Republic and Slovenia. Both cases occurred in October 2017 and involved males in their thirties.

The case reported by the Czech Republic involved a male who together with his friend had injected a substance bought on the internet as carfentanil. Blood and urine samples were positive for methoxyacetylfentanyl. The patient was hospitalised and subsequently recovered. The friend of the patient died.

The case reported by Slovenia involved a male who snorted a powder bought on the internet. The patient believed he was using ketamine. Blood and urine samples were positive for methoxyacetylfentanyl. A range of other substances were detected (methoxphenidine, benzylfentanyl, flubromazepam, diazepam, sertraline). The intoxication was considered life-threatening and required hospitalization of the patient.

Deaths

A total of 13 deaths were reported to the EMCDDA by: Belgium (1 case), Czech Republic (1), Sweden (6) ([8]), and the United Kingdom (5). Exposure to methoxyacetylfentanyl was analytically confirmed from post-mortem samples in all 13 deaths. In addition, methoxyacetylfentanyl was detected in physical samples (powder and syringes) found at the scene of death in two cases.

The deaths occurred between December 2016 and February 2018.

Of the 13 deaths, 12 were male and 1 was female. The mean age of the males was 32 years (median 32) and ranged from 25 to 41 years. The female was aged 28 years.

Cause of death

The cause of death was available in 8 cases. In 7 of the deaths, methoxyacetylfentanyl was cited (either by name or as an opioid) in the cause of death even in presence of other substances. Other substances were detected in all cases. In one case, acute ischaemic heart muscle injury was the cited cause and methoxyacetylfentanyl was present along with a benzodiazepine, norfludiazepam (desalkylflurazepam).

Methoxyacetylfentanyl was quantified in 9 cases. In the 6 cases from Sweden, post-mortem femoral blood concentrations between 18 and 76 ng/g blood were recorded (median 33 ng/g blood) ([9]). In the 2 cases from the United Kingdom, post-mortem femoral blood concentrations of 49 and 134 ng/mL were reported, and in the remaining case from the Czech Republic, a concentration of 550 ng/mL was found. 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 poly-drug use.

(8) During the course of the meeting an additional death was reported by Sweden, bringing the total number reported by Sweden to 7 cases.

(9) With ng/g being somewhat but not exactly equivalent to ng/mL.

A range of other substances were detected in the deaths, including: cocaine, cannabinoids, amphetamines, benzodiazepines, zopiclone, lamotrigine, propranolol, pregabalin, antidepressants, antipsychotics, and ethanol. Other opioids were detected in 7 of the deaths: codeine (5 deaths), morphine (5), fentanyl (3), noscapine (3), acetylfentanyl (2), furanylfentanyl (1), papaverine (1), oxycodone (1), and tramadol (1). 6-Monoacetylmorphine (heroin metabolite) was found in 3 of the 5 deaths reported by the United Kingdom.

Overall, while other substances may have contributed some toxicity, a synergistic effect with methoxyacetylfentanyl would have been likely with other central nervous system depressants such as ethanol, benzodiazepines, opioids, etc. Nevertheless, the potent opioid nature of methoxyacetylfentanyl means the primary toxic contribution could be attributed to the drug, and death may not have occurred if methoxyacetylfentanyl had not been used. An assessment of the Toxicological Significance Score (TSS) (**10**) incorporating the above considerations, shows that methoxyacetylfentanyl had a TSS value of 3 (high) in 9 out of 13 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). Three of the remaining deaths were assessed as having a TSS value of 2 (medium) and one case as having a TSS value of 1 (low).

Circumstances of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death in the cases. In the vast majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's). In one case the individual died in hospital three days following admission as a result of a cardiac arrest. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases. In 2 cases where the route of administration was known, the individuals had injected or insufflated a powder.

Deaths from other sources

In addition to deaths reported by the EMCDDA, during 2017 at least 15 deaths with confirmed exposure to methoxyacetylfentanyl were reported in the United States.

Ability to operate machinery and drive

There have been no studies of the effects of methoxyacetylfentanyl 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 methoxyacetylfentanyl.

([10]) 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

Chronic toxicity

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

Abuse liability and dependence potential

There have been no studies that have investigated the abuse liability and dependence potential of methoxyacetylfentanyl. 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl by some psychonauts. Overall, the available information does not suggest widespread use of the substance.

Methoxyacetylfentanyl 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'. While no specific examples are available, it is reasonable to assume, that, similar to other fentanils, methoxyacetylfentanyl may be supplied through the illicit heroin market. If this is the case, then most probably these individuals would not be aware that they are consuming methoxyacetylfentanyl.

Availability and quality on the market

Overall, methoxyacetylfentanyl has been detected in 11 Member States (Austria, Belgium, Czech Republic, Denmark, Finland, France, Hungary, Latvia, Slovenia, Sweden, and the United Kingdom) and Norway.

A total of 48 seizures made by law enforcement have been reported by 9 Member States (Belgium, Czech Republic, Denmark, Finland, Hungary, Latvia, Slovenia, Sweden, and the United Kingdom) and Norway. The seizures took place from June to December 2017. Methoxyacetylfentanyl has been typically seized as a powder (18 seizures; total of 180 g), as a liquid (26 seizures; total of 352 ml), and in tablet form (4 seizures; 119 tablets).

As methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl have been offered by online vendors. Some of these vendors are apparently based within the European Union.

Characteristics and behaviour of users

While no specific examples are available on the possible appeal of methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl.

Conditions under which the substance is obtained and used

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

Methoxyacetylfentanyl has also been seized as tablets.

Overall, methoxyacetylfentanyl 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 methoxyacetylfentanyl, 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl on society as a whole.

As discussed above, accidental/occupational 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 information to suggest the involvement of organised crime or established criminal groups in the manufacture, distribution and supply of methoxyacetylfentanyl.

No production sites manufacturing methoxyacetylfentanyl 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 suggests that some methoxyacetylfentanyl on the market in Europe has been produced by chemical companies based in China.

Denmark reported 1 seizure where 12.7 g of methoxyacetylfentanyl powder had been sent from China.

Belgium reported 1 seizure where the substance was seized in transit to The Netherlands.

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 methoxyacetylfentanyl 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

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

- In Czech Republic, methoxyacetylfentanyl is included in the amendment of Government Regulation No. 463/2013 Coll., which entered into force on 8 March 2018.

- In Estonia, methoxyacetylfentanyl 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 France, methoxyacetylfentanyl is controlled as of 5 September 2017.

- In Ireland, methoxyacetylfentanyl is covered by the fentanyl generic definition within the Misuse of Drugs (Amendment) Act 2015.

- In Latvia, methoxyacetylfentanyl 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, methoxyacetylfentanyl is subjected to control measures by The Republic of Lithuania Minister of Health Order No V-853 (07/07/2017) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000'.

- In Sweden, methoxyacetylfentanyl is regulated as a narcotic, as of 12 December 2017.

- In the United Kingdom, methoxyacetylfentanyl is controlled under the Misuse of Drugs Act 1971 by way of a generic definition.

- In Norway, methoxyacetylfentanyl is controlled by way of a generic definition.

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

- In Austria, methoxyacetylfentanyl is covered by the phenethylamine generic definition within the Austrian Act on New Psychoactive substances.

- In Belgium, methoxyacetylfentanyl is controlled by way of generic definition as of 6 September 2017.

- In Germany, methoxyacetylfentanyl is controlled by way of generic definition within the new psychoactive substances act (NpSG).

- In Hungary, methoxyacetylfentanyl 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, methoxyacetylfentanyl 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.

Fourteen Member States (Bulgaria, Croatia, Cyprus, 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.

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 methoxyacetylfentanyl 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 methoxyacetylfentanyl. 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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

2-Methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl) 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 methoxyacetylfentanyl is a narcotic opioid analgesic similar to fentanyl.

Similar to other opioid analgesics, the most serious acute risk arising from the use of methoxyacetylfentanyl 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 methoxyacetylfentanyl.

Methoxyacetylfentanyl has been available in Europe since at least November 2016 and has been detected in 11 Member States (Austria, Belgium, Czech Republic, Denmark, Finland, France, Hungary, Latvia, Slovenia, Sweden, and the United Kingdom) and Norway. Law enforcement seizures have been reported by 9 Member States (Belgium, Czech Republic, Denmark, Finland, Hungary, Latvia, Slovenia, Sweden, and the United Kingdom) and Norway.

A total of 13 deaths with confirmed exposure to methoxyacetylfentanyl have been reported by 4 Member States (Belgium, Czech Republic, Sweden, and the United Kingdom). In all cases, other drugs were also detected with methoxyacetylfentanyl. In at least 7 of the deaths, methoxyacetylfentanyl 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 methoxyacetylfentanyl may be under-reported since the substance is not routinely screened for in laboratories.

Methoxyacetylfentanyl is sold online as a powder in small and wholesale amounts. It is also sold as ready-to-use nasal sprays. Methoxyacetylfentanyl may also have been sold on the illicit drug market.

As with other fentanils, methoxyacetylfentanyl 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 methoxyacetylfentanyl, 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 information to suggest the involvement of organised crime in the manufacture, distribution (trafficking) and supply within the European Union.

There is limited information on the chemical precursors and the synthetic routes used to manufacture the methoxyacetylfentanyl 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 methoxyacetylfentanyl on the market in Europe has been produced by chemical companies based in China.

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

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

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

Nine Member States (Czech Republic, Estonia, Finland, France, Ireland, Latvia, Lithuania, Sweden, and the United Kingdom) and Norway control methoxyacetylfentanyl under drug control legislation. Five Member States (Austria, Belgium, Germany, Hungary, and Poland) control methoxyacetylfentanyl under other legislation.

As for any new psychoactive substance, many of the questions related to methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, since methoxyacetylfentanyl was first detected at least thirteen 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 methoxyacetylfentanyl to users, practitioners, policy makers, decision makers, and those who may be at risk of occupational exposure.

11. List of annexes

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

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

ANNEX 1

DRAFT

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

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

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* ([11]) on 12 October 2017, the EMCDDA and Europol launched the Joint Report procedure for 2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl) 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl.

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 methoxyacetylfentanyl as well as a similarity search. Structural and text-based searches in SureChEMBL patent database were also performed.
Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information),, and in English-language online drug forums. The search terms used were: ‘methoxyacetylfentanyl’; ‘methoxyacetyl fentanyl’; ‘methoxyacetyl-F’; ‘methoxy-AF’; ‘methoxy-AcF’.
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.

([11]) 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 ([12]), Rachel Christie ([3]), Joanna de Morais ([3]), Rita Jorge ([3]), Anabela Almeida ([3]), Sofía Sola ([3]), Ana Gallegos ([3]), Michael Evans-Brown ([13]), 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.

([12]) Alere Forensics, Malvern, Worcestershire, United Kingdom.
([13]) 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

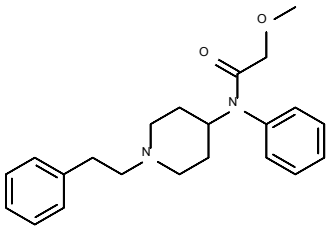
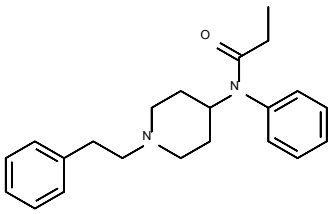
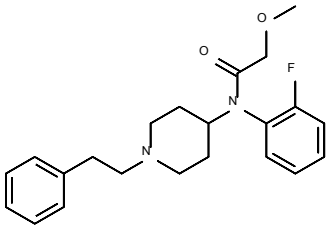
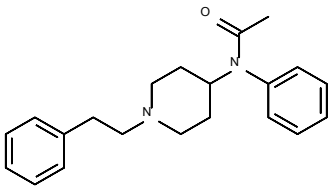
Chemical description and names

2-Methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl) is structurally related to fentanyl ([14]), 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.
Methoxyacetylfentanyl differs from fentanyl by the addition of an oxygen atom in the propionamide group. Methoxyacetylfentanyl is also structurally related to ocfentanil, which was recently recommended for international control ([15]). Ocfentanil contains an additional fluorine atom at the 2-position of the phenyl ring attached to the carboxamide (Figure 1). Other close structural derivatives of methoxyacetylfentanyl under international control include acetylfentanyl ([16]).
Methoxyacetylfentanyl differs from acetylfentanyl by the addition of a methoxy group in the acetamide moiety.

A total of fifteen fentanils are controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol ([17]).

([14]) Systematic name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidinyl-4-yl]propanamide.
([15]) The 39th meeting of the Expert Committee on Drug Dependence (ECDD) critically reviewed *N*-(2-fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (ocfentanil) in November 2017 and has recommended that the substance is placed in Schedule I of the Single convention on Narcotic Drugs (1961) (World Health Organisation, 2017).
([16]) Systematic chemical name: *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacetamide. The substance was included in Schedule I and IV of the 1961 Single Convention on Narcotic Drugs, by decision of the Commission on Narcotic Drugs (CND) during its 59th Session, on 17 May 2016.
([17]) 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 methoxyacetylfentanyl. Information on fentanyl, ocfentanil, and acetylfentanyl are provided for comparison.

		
	methoxyacetylfentanyl	fentanyl
Molecular formula	$C_{22}H_{28}N_2O_2$	$C_{22}H_{28}N_2O$
Molecular mass	352.48	336.48
		
	ocfentanil	acetylfentanyl
Molecular formula	$C_{22}H_{27}FN_2O_2$	$C_{21}H_{26}N_2O$
Molecular mass	370.47	322.44

Names and other identifiers

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

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

Chemical Abstract name:
acetamide, 2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-
Other 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-piperidinyl]-acetamide;
N-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]-2-methoxyacetamide;
N-[1-(2-phenylethyl)-4-piperidinyl]-2-methoxyacetanilide
Chemical Abstract Service Registry Numbers (CAS RNs) ([18]):
101345-67-9 (free base)
101365-54-2 (hydrochloride salt)
130820-21-2 (maleate salt)
PubChem CID ([19])*:*
968688
IUPAC International Chemical Identifier Key (InCHI Key) ([20]):
SADNVKRDSWWFTK-UHFFFAOYSA-N
SMILES ([21]):
O=C(COC)N(C1=CC=CC=C1)C(CC2)CCN2CCC3=CC=CC=C3
COCC(=O)N(C2CCN(CCc1ccccc1)CC2)c3ccccc3
Common names:

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

Stree/user names and/or sold as:

'MAF' (Belgium), 'methoxy' (Belgium), 'synthetic heroin' (Belgium)

([18]) 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.
([19]) National Center for Biotechnology Information. PubChem Compound Database; CID=968688, https://pubchem.ncbi.nlm.nih.gov/compound/968688 (accessed Jan. 23, 2018).
([20]) InChI Key is a unique, non-proprietary structural identifier of chemical substances used in electronic sources.
([21]) The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

Identification and analytical profile

Physical description

Methoxyacetylfentanyl contains one 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 brown powder (Slovenian National Forensic Laboratory, 2016). Its citrate salt has been described as a white powder. The reported melting point of its free base is 96–97°C, while the maleate salt has a melting point of 141–142°C (Jílek et al., 1990).
The hydrochloride and citrate salt of methoxyacetylfentanyl are soluble in dichloromethane, methanol and water (Slovenian National Forensic Laboratory, 2016; Slovenian National Forensic Laboratory, 2017). No solubility data are available regarding the free base of methoxyacetylfentanyl, but given its similarity to fentanyl, it is expected to be lipophilic ([22]) and sparingly soluble in water.
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 C.

Chemical stability and typical reactions

The material safety data sheet for methoxyacetylfentanyl from the Cayman Chemical Company specifies that the compound is stable and does not undergo polymerization (Cayman Chemical Company, 2016). No other information is known regarding the stability of the substance.

Analytical profile

Analytical data for methoxyacetylfentanyl are available in the literature. Methoxyacetylfentanyl is commercially available as a certified reference standard ([23]). 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; Jílek et al., 1990; Wilde et al., 2017), and nuclear magnetic resonance (Jílek et al., 1990; Slovenian National Forensic Laboratory, 2016). A direct analysis in real time ion source coupled to a time-of-flight mass spectrometer (DART-TOF MS) of a series of fentanils, including methoxyacetylfentanyl, has also been reported (Shonsey, 2017). The urinary analysis of methoxyacetylfentanyl and other synthetic opioids by solid phase extraction (SPE) followed by HPLC-MS/MS was recently published (UCT, 2017).

([22]) LogP provides a measure of lipophilicity of a compound. The predicted LogP values for methoxyacetylfentanyl and fentanyl are 2.57 and 3.68 respectively (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).

([23]) At least 13 vendors/suppliers of methoxyacetylfentanyl listed on the Open Chemistry Database (PubChem, 2018). Additionally, Cayman Chemicals lists methoxyacetylfentanyl in its catalogue (https://www.caymanchem.com/product/23540).

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.
Drug screenings using enzyme-linked immunoassays (ELISA) and LC/MS have detected a series of fentanils including methoxyacetylfentanyl (Yong et al., 2017).
A recent study examining the detectability of a series of fentanils noted about 80% cross-reactivity of methoxyacetylfentanyl in three immunoassays developed for the urinary assay for fentanyl (Helander et al., 2018). In addition, LSD immunoassays may detect methoxyacetylfentanyl (Gagajewski et al., 2002). Identification of methoxyacetylfentanyl requires confirmatory analysis (US DEA, 2017a).

Methods and chemical precursors used for the manufacture

The synthesis of methoxyacetylfentanyl was first described by Huang and co-workers in the context of an investigation of fentanyl derivatives with central nervous system depressant properties (Huang et al., 1985). The synthetic pathway used NPP (**[24]**) and aniline as precursors to yield ANPP (**[25]**), which was then reacted with methoxyacetyl chloride (**[26]**) to yield methoxyacetylfentanyl.
Subsequent work by Jílek and co-workers (Jílek et al., 1990; Jílek et al., 1992) used a one-step method with ANPP, 2-methoxyacetic anhydride and ammonium hydroxide to produce methoxyacetylfentanyl.
In addition to these synthetic routes and precursors, methods used to manufacture pharmaceutical fentanyl are generally applicable to the synthesis of methoxyacetylfentanyl, given the structural similarity between the two compounds (Casy and Huckstep, 1988; Gupta et al., 2013; Zee and Wang, 1980). 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 (**[27]**). 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 steps 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.

(**[24]**) The systematic name for NPP, a common pre-precursor to fentanyl and several of its derivatives, is *N*-phenethyl-4-piperidone. NPP can be synthesized from piperidone and phenethyl-tosylate or phenethyl-bromide through a simple SN_2-type substitution (Siegfried, n.d.).

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

(**[26]**) Methoxyacetyl chloride is readily available in bulk quantities as it is used in the manufacture of agrochemicals (e.g., the fungicide metalaxyl), pharmaceuticals (e.g., mibefradil) and diagnostic agents (e.g., iopromide).

(**27**) 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).

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, 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 methoxyacetylfentanyl that has been detected on the European drug market.

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, methoxyacetylfentanyl has been detected in powders and liquids, and, to a lesser extent, in tablets. Some of the liquids were detected in nasal sprays and in syringes.
Forensic laboratories usually do not report whether methoxyacetylfentanyl present in seizures/collected samples is in its free base or salt form.

A1.3. Route of administration and dosage

As with other fentanils, methoxyacetylfentanyl 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). In one of the seizures reported to the EMCDDA, methoxyacetylfentanyl was detected in a liquid contained in a nasal spray.

Dosage

Limited information is available regarding the dose and the dose regimens of methoxyacetylfentanyl. 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 methoxyacetylfentanyl are limited to non-clinical studies. These data suggest that methoxyacetylfentanyl 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 methoxyacetylfentanyl and its metabolites.

Pharmacodynamics

In vitro studies

Pharmacological data on methoxyacetylfentanyl have been published recently by the United States Drug Enforcement Administration (US DEA, 2017a).
The binding affinity (K_i) ([28]) 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).
The currently available data suggests that methoxyacetylfentanyl binds to the μ-opioid receptor (MOR) with high selectivity (Ki = 0.56 ± 0.081 nM; [^{3}H]DAMGO used as a radioligand) over the δ- and κ- opioid receptors (DOR and KOR) with Ki values of 1,530 ± 110 nM ([^{3}H]DPDPE used as radioligand) and 907 ± 74 nM ([^{3}H]U69,593 used as radioligand), respectively.

An *in vitro* functional assay found that methoxyacetylfentanyl (EC_{50} = 51.9 ± 4.7 nM) ([**29**]) has μ-opioid receptor agonist activity, similar to morphine (EC_{50} = 23.2 ± 3.6 nM) and fentanyl (EC_{50} = 16.4 ± 2.4 nM). Methoxyacetylfentanyl showed low potency in DOR and KOR receptor preparations ([^{35}S]GTPγS binding functional assay) with EC_{50} = 1,390 ± 460 nM and EC_{50} = 1,460 ± 470 nM, respectively, suggesting MOR selective profile.

Together, these *in vitro* studies suggest that methoxyacetylfentanyl is a μ-opioid receptor agonist. It is not known, however, to what extent this agonist effect would translate to high toxicity *in vivo*. The effect of methoxyacetylfentanyl on pharmacological targets other than the three opioid receptor subtypes is not known.

Animal studies

Three studies that have investigated the antinociceptive activity of methoxyacetylfentanyl in mice have been reported in the scientific literature.
Following intravenous administration (tail vein), methoxyacetylfentanyl displayed antinociceptive effects using the mouse hot plate test (58°C). The ED_{50} value was determined as 0.08 mg/kg although data for comparator substances, such as morphine and fentanyl, were not reported. The patent gives an ED_{50} of 0.02 mg/kg for furanylfentanyl and 0.0077 mg/kg for ocfentanil ([**30**]) (Huang et al., 1986).

([28]) K_i in a binding assay is defined as the affinity constant of a displacer compound for the receptor.
([**29**]) EC_{50} is the effective concentration at 50% maximal response.
([**30**]) *N*-(2-Fluorophenyl)-2-methoxy-*N*-(1-(2-phenylethyl)-4-piperidinyl)acetamide.

In a paper published by Bagley et al. (1991) the ED_{50} value for methoxyacetylfentanyl was reported to be 0.053 mg/kg (90% confidence intervals: 0.025–0.114) in the mouse hot-plate test (55 ºC), compared to 0.018 mg/kg (90% confidence intervals: 0.014–0.023) for fentanyl.

The analgesic effects of methoxyacetylfentanyl in the form of hydrogen maleate have been studied in mice (the doses given were calculated per base) (Jílek et al., 1990; Jílek et al., 1992). In the peritoneal test in mice (inhibition of the writhing syndrome induced by a noxious chemical stimulus) subcutaneous dose 0.1 mg/kg of methoxyacetylfentanyl was active in 90% of the animals (fentanyl at 0.01 mg/kg active in 80%). In the Haffner's tail clip method, which uses a noxious mechanical stimulus, methoxyacetylfentanyl was inactive at 1 mg/kg following subcutaneous administration to mice (for fentanyl D_{50} = 0.06 mg/kg s.c.; pethidine as a reference substance ED = 2.5 mg/kg i.v.).

Pharmacokinetics

Due to its lipophilicity (Section A1.1.), methoxyacetylfentanyl, 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.
Information on the pharmacokinetics of methoxyacetylfentanyl appears to be limited to a recent *in vitro* study that examined the metabolism of the substance. According to this study (Wilde et al., 2017) which used a human liver microsomal preparation, a characteristic metabolic step for methoxyacetylfentanyl appears to be *O*-demethylation leading to 2-hydroxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide. *N*-desalkylation, hydroxylation of the piperidine ring and the phenylethyl side chain, *N*-oxidation, as well as amide hydrolysis to 4-ANPP were also observed. The extent to which the biotransformation products of methoxyacetylfentanyl are comparable to closely related analogues remains to be investigated. It seems likely that some overlap might exist, including the amide hydrolysis product 4-ANPP (Watanabe et al., 2017; Wilde 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 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl could not be identified, although it seems conceivable that interactions observed with fentanyl might equally apply (Preston, 2016). For example, should methoxyacetylfentanyl 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 ([31]) may result in increased plasma concentration of methoxyacetylfentanyl. This could increase the risk of poisoning, including potentially fatal respiratory depression.
The concomitant use of other central nervous system (CNS) depressants with methoxyacetylfentanyl, 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) or 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 which act on the serotonergic system. It is not known if this association with serotonin syndrome is also seen with methoxyacetylfentanyl.

Effects on ability to drive and operate machines

No studies of the effects of methoxyacetylfentanyl 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 methoxyacetylfentanyl.

A3. Psychological and behavioural effects

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

Methoxyacetylfentanyl 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 methoxyacetylfentanyl is used for other legitimate purposes.

([31]) 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

There are no reported uses of methoxyacetylfentanyl 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 methoxyacetylfentanyl returned no results.
There is no marketing authorisation (existing, on-going or suspended) for methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl in animal models.

B2. Human data

No studies were identified that have investigated the dependence and/or abuse potential of methoxyacetylfentanyl in humans.
While no specific data exist for methoxyacetylfentanyl, 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 methoxyacetylfentanyl.

Section C. Prevalence of use

Information from seizures, collected and biological samples

Methoxyacetylfentanyl was formally notified on 9 December 2016 by the EMCDDA on behalf of the Slovenia, in accordance with Article 4 of the Council Decision. The Reporting Form details the detection of methoxyacetylfentanyl in a sample of 5 g of brown powder, purchased from the Internet on 14 November 2016, as part of the EU-funded project Response. 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).
In total, 11 Member States (Austria, Belgium, Czech Republic, Denmark, Finland, France, Hungary, Latvia, Slovenia, Sweden, and the United Kingdom) and Norway reported detections of methoxyacetylfentanyl ([32]) (EMCDDA, 2017a).

([32]) '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

It is important to note that methoxyacetylfentanyl may be under-detected and under-reported 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.

Information from seizures

In total, 48 seizures of methoxyacetylfentanyl ([33]) were reported to the EMCDDA by 9 Member States and Norway. These were: Belgium (1 case), Czech Republic (1), Denmark (1), Finland (1), Hungary (1), Latvia (5), Slovenia (1), Sweden (30), the United Kingdom (3), and Norway (4). The seizures took place from June to December 2017 and were made by police or customs agencies. Methoxyacetylfentanyl was detected in powders and liquids, and, to a lesser extent, in tablets. The exact composition or purity of the seized substance, including the presence of any adulterants or cutting agents, however, is rarely reported.

Powders

A total of 180 g of powder containing methoxyacetylfentanyl was seized in 18 cases. The cases were reported by: Belgium (1 case), Czech Republic (1), Denmark (1), Finland (1), Hungary (1), Latvia (4), Slovenia (1), Sweden (5), and the United Kingdom (3). Sweden accounted for almost 90% of the quantity seized (159.6 g). Briefly:

- Where known, the powders were reported to be white or off-white.

- In the large majority of cases, methoxyacetylfentanyl was the only substance detected in the powders.

- In most of the cases, the quantities seized were below 3 g.

- The largest single seizure was reported by Swedish customs and consisted of 48.9 g. Danish customs reported a single seizure of 12.7 g that originated from China.

- In the case reported by the Czech Republic, methoxyacetylfentanyl was detected along with alprazolam in a powder that had been purchased on the internet as ‘carfentanil’. The powder was found at the scene of a non-fatal intoxication and a death (Section D1.2). In addition, 2 syringes were also found; one contained methoxyacetylfentanyl, the other contained methoxyacetylfentanyl, methamphetamine and alprazolam. In the case reported by Hungary a powder containing methoxyacetylfentanyl was found at the scene of a death.

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purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).

([33]) 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 seizure reported by Slovenia, 0.11 g of methoxyacetylfentanyl (as its citrate salt) was detected in a 'legal high' type product labelled as 'Ching' which was purchased by a user from the internet (Annex 1). A number of other new psychoactive substances were also seized in the same case, including other opioids ('benzylfentanyl').

- In a case reported by Latvia, methoxyacetylfentanyl was detected along with methadone.

Liquids
A total of 352 mL of liquid containing methoxyacetylfentanyl was seized in 26 cases that were reported by: Latvia (1 case), Sweden (21), and Norway (4). Sweden accounted for just over 80% of the total quantity seized (292 mL).
In the case reported by Latvia, the liquid was recovered from a syringe. In the cases reported by Norway, the liquids were found in nasal sprays.
Tablets
A total of 119 tablets containing methoxyacetylfentanyl were seized in 4 cases, all of which were reported by Sweden.

Information from collected samples

A total of 5 collected samples containing methoxyacetylfentanyl were reported by: Austria, Belgium, France, Slovenia, and the United Kingdom. Briefly:

- In the case reported by Belgium, the sample also contained cocaine and was found at the scene of a death. It is unknown if the powder was purchased as cocaine.

- In the remaining cases, the samples were purchased as a powder on the internet.

    - In the case reported by Slovenia, a test purchase was made from a vendor in China.

    - In the case reported by Austria, a user intended to purchase '4-HO-MET' and received a powder containing 4-HO-MET and methoxyacetylfentanyl.

    - In the case reported by France, the user purchased the substance on the darknet as 'fentanyl' and submitted the sample for testing because the 'cheap' price of sale elicited suspicion (17€/100 mg).

    - In the case reported by the United Kingdom, a test purchase was made from best-feel.com.

Information from biological samples

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

Availability, supply, price

The available information suggests that methoxyacetylfentanyl is typically sold online 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'.
Of note, is that one seizure that was reported concerned the detection of methoxyacetylfentanyl in a 'legal-high' type product. The product was labelled as 'Ching', and such products have been sold as 'legal' replacements for cocaine in Europe for a number of years (Annex 1).

Availability from Internet vendors

Methoxyacetylfentanyl is sold on the surface web, typically as a powder and as a solution in ready-to-use nasal sprays.
Sweden reported that the availability of methoxyacetylfentanyl in the country is linked to two known vendors, who sell substances on several domestic sites 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.
In addition, Austria, Slovenia, and the United Kingdom also reported instances where methoxyacetylfentanyl was purchased from the surface web.
Information on the availability of methoxyacetylfentanyl on the darknet is limited to a single report from France (see above).

Prevalence of use

No studies were identified that have investigated the prevalence of use of methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl by some psychonauts. Overall, the available information does not suggest widespread use of the substance.
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 methoxyacetylfentanyl 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 of methoxyacetylfentanyl is limited to a single study in mice (Jílek et al., 1992). This study reported an LD_{50} value of 38 mg/kg following intravenous administration. The following toxic effects were also reported: dyspnea, loss of the righting reflex, transient convulsive symptoms, and Straub phenomenon. While no comparative standard was used in this particular study, data from a different study has reported an LD_{50} value for fentanyl of 11.2 mg/kg (7.4–16.8, 95% fiducial limits) following intravenous administration to mice (Gardocki and Yelnosky, 1964).

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of methoxyacetylfentanyl and/or its metabolites in humans. Although the pharmacology and toxicology of methoxyacetylfentanyl 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, and respiratory depression or 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 methoxyacetylfentanyl 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) ([34]).

There is lack of information on the clinical features of poisoning caused by methoxyacetylfentanyl. Nonetheless, the available data suggests that the nature of the effects of methoxyacetylfentanyl 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, respiratory depression and arrest.
Data from serious adverse events associated with methoxyacetylfentanyl are discussed below.

([34]) 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.

Acute intoxications reported by the Member States

Two cases of acute intoxication with confirmed exposure to methoxyacetylfentanyl were reported to the EMCDDA by Czech Republic (1) and Slovenia (1) ([35]). Both cases occurred in October 2017 and involved males in their thirties.
The case reported by Czech Republic involved a male, who, together with his friend, had injected a substance bought on the internet as carfentanil (Section C). Two syringes were found at the scene; one contained only methoxyacetylfentanyl, while the other contained methamphetamine, methoxyacetylfentanyl, and alprazolam. The patient was hospitalised and subsequently recovered. Blood and urine samples were positive for methoxyacetylfentanyl. The friend of the patient died.
The case reported by Slovenia involved a male who snorted a powder bought on the internet. The patient believed he was using ketamine. Blood and urine samples were positive for methoxyacetylfentanyl. A range of other substances were detected in the biological sample (methoxphenidine, benzylfentanyl, flubromazepam, diazepam, sertraline). The intoxication was considered life-threatening and required hospitalization of the patient.

Acute intoxications identified from other sources

No cases of acute intoxication were identified from other sources.

Deaths reported by the Member States

A total of 13 deaths were reported to the EMCDDA by: Belgium (1), Czech Republic (1), Sweden (6 cases), and the United Kingdom (5) ([36]). Exposure to methoxyacetylfentanyl was analytically confirmed from post-mortem samples in all 13 deaths. In addition, methoxyacetylfentanyl was detected in physical samples (powder and syringes) found at the scene of death in two cases.
The deaths occurred between December 2016 and February 2018.
Of the 13 deaths, 12 were male and 1 was female. The mean age of the males was 32 years (median 32) and ranged from 25 to 41 years. The female was aged 28 years.

([35]) In addition, Sweden reported 3 acute intoxications with suspected exposure to methoxyacetylfentanyl. These cases are not discussed further in this report

([36]) Hungary reported a seizure of a powder containing methoxyacetylfentanyl that was found at the scene of a death. The death has not been formally reported and therefore it 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 cases. In the vast majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's). In one case the individual died in hospital three days following admission as a result of a cardiac arrest. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases. In 2 cases where the route of administration was known, the individuals had injected or insufflated a powder.

The cause of death was available in 8 cases. In 7 of the deaths, methoxyacetylfentanyl was cited (either by name or as an opioid) in the cause of death even in presence of other substances. Other substances were detected in all cases. In one case, acute ischaemic heart muscle injury was the cited cause and methoxyacetylfentanyl was present along with a benzodiazepine, norfludiazepam (desalkylflurazepam).

Methoxyacetylfentanyl was quantified in 9 cases. In the 6 cases from Sweden, post-mortem femoral blood concentrations between 18 and 76 ng/g blood were recorded (median 33 ng/g blood) (with ng/g being somewhat but not exactly equivalent to ng/mL). In the 2 cases from the United Kingdom, post-mortem femoral blood concentrations of 49 and 134 ng/mL were reported, and in the remaining case from the Czech Republic, a concentration of 550 ng/mL was found. 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 poly-drug use.

A range of other substances were detected in the deaths, including: cocaine, amphetamines, benzodiazepines, zopiclone, lamotrigine, pregabalin, antidepressants, antipsychotics, and ethanol. Other opioids were detected in 7 of the deaths: codeine (5 deaths), morphine (5), fentanyl (3), noscapine (3), acetylfentanyl (2), furanylfentanyl (1), papaverine (1), oxycodone (1), and tramadol (1). 6-Monoacetylmorphine (heroin metabolite) was found in 3 of the deaths.

Overall, whilst other substances may have contributed some toxicity, a synergistic effect with methoxyacetylfentanyl would have been likely with other central nervous system depressants such as ethanol, benzodiazepines, opioids, etc. Nevertheless, the potent opioid nature of methoxyacetylfentanyl means the primary toxic contribution could be attributed to the drug and death may not have occurred if methoxyacetylfentanyl had not been used. An assessment of the Toxicological Significance Score (TSS) (Elliott, Sedefov, and Evans-Brown, 2018) incorporating the above considerations, shows that methoxyacetylfentanyl had a TSS value of 3 (high) in 9 out of 13 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). Three of the remaining deaths were assessed as having a TSS value of 2 (medium) and one case as having a TSS value of 1 (low).

Deaths identified from other sources

The United States Drug Enforcement Administration reported 2 confirmed deaths associated with methoxyacetylfentanyl that occurred in 2017. The deaths occurred in Pennsylvania, United States (US DEA, 2017a; US DEA, 2017b).
Smith and Kinkaid reported identification of methoxyacetylfentanyl in 3 deaths in Allegheny County, Pennsylvania, United States ([37]) (Smith and Kinkaid, 2017).
Beck et al. reported that "methoxy acetyl fentanyl" was identified in 10 deaths in Jefferson County, Alabama, United States. The mean concentration of methoxyacetylfentanyl was 0.110 mg/L with a median of 0.014 mg/L (Beck et al., 2017). The authors noted that in the first 4 deaths, the concentrations of methoxyacetylfentanyl were substantially higher (ranging from 0.132 mg/L to 0.449 mg/L) to the remaining 6 deaths that occurred two weeks later, (ranging from 0.005 mg/mL to 0.011 mg/L). The authors speculate that the reason for these concentration differences was that initially methoxyacetylfentanyl was added into the heroin supply at high doses to generate demand, and that once the reputation, and therefore demand, for methoxyacetylfentanyl was established, the amount added was reduced.

D2. Chronic health effects

D2.1. Animal data

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

D2.2. Human data

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

D3. Factors affecting public health risks

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

Methoxyacetylfentanyl 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'. Methoxyacetylfentanyl is also used to make tablets, as evidenced by the seizures by Swedish Police.
The available information also suggests that cyclopropylfentanyl has been mis-sold as methoxyacetylfentanyl.

([37]) Two of the deaths reported by Smith and Kinkaid may be duplicates with the cases reported by the United States Drug Enforcement Administration (US DEA, 2017a).

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 methoxyacetylfentanyl and its effects are limited.

D3.3. Characteristics and behaviour of users

While no specific examples are available on the possible appeal of methoxyacetylfentanyl 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 methoxyacetylfentanyl is used in the home environment. In fact, iIn the majority of the deaths the individuals were found dead. It appears that in at least some of these cases the poisoning with methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 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 (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 methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl is obtained and used. Methoxyacetylfentanyl is offered for sale on the surface web, typically as powders and ready-to-use nasal sprays. It has also been seized as tablets.

Section E. Social Risks

While there have been no studies on the social risks of methoxyacetylfentanyl, it is likely that some of the risks are similar to those associated with illicit use of 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 methoxyacetylfentanyl. Given that methoxyacetylfentanyl 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 methoxyacetylfentanyl on the direct social environment. Given that methoxyacetylfentanyl 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 methoxyacetylfentanyl 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 methoxyacetylfentanyl.

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

There are no data on the possible effects of methoxyacetylfentanyl 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 methoxyacetylfentanyl to specific user groups (aside from psychonauts), it is reasonable to assume methoxyacetylfentanyl 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 methoxyacetylfentanyl, 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 methoxyacetylfentanyl.
There are indications that production of fentanils such as methoxyacetylfentanyl 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 methoxyacetylfentanyl in Europe.

Sweden reported that while there is no known production in the country, similar to the supply of other fentanils, the methoxyacetylfentanyl 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 methoxyacetylfentanyl.
Sweden reported that the substance 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.
Denmark reported 1 seizure where 12.7 g of methoxyacetylfentanyl powder had been sent from China. Belgium reported 1 seizure where the substance was seized in transit to The Netherlands.

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 methoxyacetylfentanyl 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 mis-sold as methoxyacetylfentanyl in some circumstances. In addition, in a small number of cases, methoxyacetylfentanyl has been mis-sold as other illicit substances and/or found in mixtures with other illicit substances.

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 methoxyacetylfentanyl.

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 methoxyacetylfentanyl.

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 methoxyacetylfentanyl.

F

6. 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 methoxyacetylfentanyl.

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 methoxyacetylfentanyl.

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 methoxyacetylfentanyl.

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Annex 1

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

Images from seizures and collected samples provided to the EMCDDA

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

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

Anabela ALMEIDA
Action on new drugs sector, Risks to public safety and security unit

Rachel CHRISTIE
Action on new drugs sector, Risks to public safety and security unit

Ana GALLEGOS
Action on new drugs sector, Risks to public safety and security unit

Rita JORGE
Action on new drugs sector, Risks to public safety and security unit

Joanna de MORAIS
Action on new drugs sector, Risks to public safety and security unit

Sofía SOLA
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