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Furanylfentanyl

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

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

About this series

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

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

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1. Introduction

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

In November 2016, the EMCDDA and Europol examined the available information on the new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]-furan-2-carboxamide, commonly known as furanylfentanyl, through a joint assessment based upon the following criteria:

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

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

2. Information collection process

In compliance with the provisions of the Council Decision, on 16 November 2016 the EMCDDA and Europol launched a procedure for the collection of information on furanylfentanyl, in order to prepare the Joint Report. The information was collected mainly through the Reitox National Focal Points in the Member States, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway, Iceland and Liechtenstein. The EMA also provided information as relevant to the centralised procedure for authorising medicinal products. The information collection process was largely concluded by 28 December 2016.

Information collected by Europol

Europol asked the Europol National Units to provide information on:

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

Europol received responses from 19 Member States ⁽²⁾ and Norway.

Information collected by the EMA

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

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

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

Furthermore, in anticipation of Article 7.3 of the Council Decision in relation to the manufacturing of medicinal

⁽²⁾ In alphabetical order: Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Slovenia, Spain and Sweden.

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

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

products in the European Union, the EMA also requested information on whether the new psychoactive substance furanylfentanyl is used to manufacture a medicinal product:

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

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

Information collected by the EMCDDA

The EMCDDA collected information through:

1. a structured questionnaire to the Reitox National Focal Points. The EMCDDA received replies from all 28 Member States, as well as Turkey and Norway;
2. reports previously provided to the European Union Early Warning System, including EMCDDA–Europol Reporting Forms and Progress Reports and Final Reports;
3. routine monitoring of open source information;
4. a specific information request to the World Health Organization on whether or not furanylfentanyl is under assessment by the United Nations system; and,
5. a search of open source information conducted specifically for the production of the Joint Report which included: scientific and medical literature, official reports, grey literature, internet drug discussion forums and related websites (hereafter, 'user websites'), and, online vendors selling furanylfentanyl.

Thus, the information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part). The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. Images of the seizures and collected samples reported to the EMCDDA and Europol are provided in Annex 1 and Annex 2, respectively.

3. Information required by Article 5.2 of the Council Decision

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

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

Chemical description and names

Furanylfentanyl belongs to the 4-anilidopiperidine class of synthetic opioids. This class also includes fentanyl, acetylfentanyl ⁽⁵⁾⁽⁶⁾ and a number of other fentanils, which are internationally controlled.

Furanylfentanyl differs from fentanyl due to the presence of a furan ring in place of an ethyl group attached to the carbonyl.

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

Furanylfentanyl has one positional isomer, which is 3-furanylfentanyl. In 3-furanylfentanyl, the carboxamide is attached to the 3-position of the furan ring.

The synthesis of furanylfentanyl was first described in a 1986 patent (Huang et al., 1986).

Commonly used names: furanylfentanyl

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

Chemical Abstracts names: N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-2-furancarboxamide

Other chemical names: 1-(2-phenylethyl)-4-(N-phenyl-2-furoylamido)piperidinium, N-(1-phenethylpiperidin-4-yl)-N-phenylfuran-2-carboxamide, N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]-2-furamide, N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylfuran-2-carboxamide

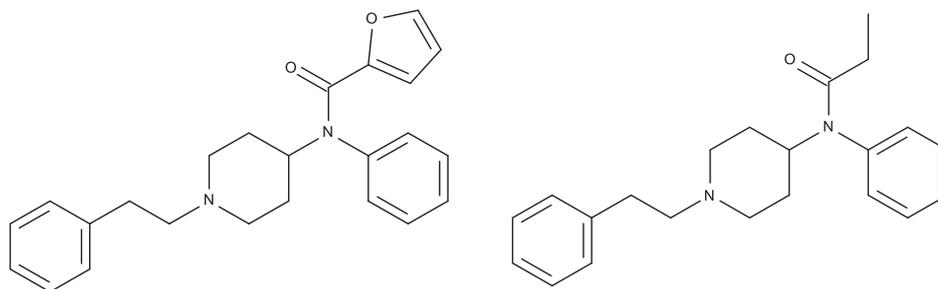
⁽⁴⁾ Austria, Belgium, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Latvia, the Netherlands, Norway, Slovakia, Spain and Sweden provided a response in relation to human and veterinary medicinal products. Croatia, Czech Republic, Italy and the United Kingdom provided a response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

⁽⁵⁾ N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]acetamide.

⁽⁶⁾ Schedule I and IV of the 1961 United Nations Single Convention on Narcotic Drugs.

FIGURE 1

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



	furanylfentanyl	fentanyl
Molecular formula	C ₂₄ H ₂₆ N ₂ O ₂	C ₂₂ H ₂₈ N ₂ O
Molecular mass	374.48	336.48

Other names and code names: FU-F, 2-furanylfentanyl, despropionyl furanoyl fentanyl, furanyl fentanyl, Furanylfenta and furanyylifentanyyli (Finnish).

Names for products in herbal form seized in Poland are: 'talizman motocyklisty', 'Talizman 0,5g-Ziel' and 'Talizman 1,0g – Ziel' (section 3.2.2).

Chemical Abstracts Service (CAS) registry numbers (7):

101345-66-8: base

101365-56-4: hydrochloride salt

IUPAC International Chemical Identifier Key (InChI Key) (8):

FZJVHWISUGFFQV-UHFFFAOYSA-N

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

Physical description

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

There is no solubility data on furanylfentanyl or its hydrochloride salt; due to its similarity to fentanyl, the free

base could be expected to be sparingly soluble in water; the hydrochloride and citrate salt could be expected to have greater aqueous solubility.

Furanylfentanyl is expected to be lipophilic. Similarly to acryloylfentanyl (EMCDDA, 2016), it could be expected that carry-over of traces of the substance during sample handling and analysis could be problematic (Degg, 2014).

Furanylfentanyl has been typically seized in powder form however it has also been detected to a lesser extent in liquid (often in nasal spray bottles), tablet and herbal material form. A more detailed description of seizures and collected samples can be found in section 3.2.1 and section 3.2.2.

Detection and analysis

Methods documented in the literature for the detection of furanylfentanyl include: liquid chromatography – tandem mass spectrometry (LC-MS/MS), liquid chromatography – high resolution-mass spectrometry (LC-HRMS) (Helander et al., 2016; Mohr et al., 2016), gas chromatography – mass spectrometry (GC-MS), high performance liquid chromatography time-of-flight (HPLC-TOF), Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR) and nuclear magnetic resonance (NMR) (Slovenian National Forensic Laboratory, 2016).

The implementation of chromatographic techniques, infrared and nuclear magnetic resonance spectrometry allow unambiguous differentiation between 2- and 3-furanylfentanyl. As of January 2017, the detection of 3-furanylfentanyl in Europe has not been reported to the EMCDDA.

(7) 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.

(8) InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

It is possible that immunoassays for fentanyl may not distinguish between furanylfentanyl and fentanyl due to the structural similarity between the two substances (US DEA, 2016b). Identification of furanylfentanyl therefore would require further confirmatory analysis, such as mass spectrometry (US DEA, 2016b). Similarly, furanylfentanyl is not expected to give a positive response to tests developed for morphine-type opioids. There is no information on the reaction of furanylfentanyl to presumptive colour tests.

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

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

3.2.1 Information provided to Europol

Europol received replies from 19 Member States (Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Slovenia, Spain and Sweden) and Norway.

Nine countries reported that they have no available information on furanylfentanyl (Belgium, Croatia, Greece, Hungary, Ireland, Italy, Latvia, Lithuania and Spain).

Eleven countries provided information on furanylfentanyl (Austria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Luxembourg, Slovenia, Sweden and Norway).

The United States also provided information to Europol on furanylfentanyl seizures.

The level of production

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

Sweden reported that furanylfentanyl is ordered in powder form from China and then sent to Sweden, either directly or via other EU Member States. Further handling is performed by persons involved in the sale, for example converting it to liquid form and placing it into unmarked spray bottles of different colours ordered from China (as documented in the Joint Report on acryloylfentanyl) (EMCDDA, 2016). According to

Swedish authorities, there are a small number of people who are involved in the trafficking of furanylfentanyl in Sweden. In general, the same manufacturing and supply chains that deal with other fentanyl derivatives apply to furanylfentanyl. Sweden also reported that one of the biggest on-line vendors, thesmack.biz, offered furanylfentanyl for sale but in most cases the products contained fentanyl instead.

The level of distribution

A total of 32 seizures were reported by 9 Member States (Austria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Luxembourg and Sweden).

Austria

Austria reported 2 seizures, 0.4 grams of white powder and 15.9 ml of colourless liquid ordered from the internet (origin unknown).

Cyprus

Cyprus reported 1 seizure which occurred in 2016. In the seizure, 0.87 grams of furanylfentanyl and 0.34 grams of butyrylfentanyl were detected.

Czech Republic

Czech Republic reported 1 seizure of furanylfentanyl but without additional information. A photo showing how the substance was packaged was provided (Annex 2). No other information was provided.

Denmark

Denmark reported 1 small seizure of furanylfentanyl, which occurred in November 2016. No other details were provided.

Estonia

Estonia reported 10 seizures of furanylfentanyl. All the seizures were in powder form, and most of them were under 1 gram each. The largest seizure was 50 grams, which arrived in Estonia from Poland en-route from China in a postal parcel.

Finland

Finland reported 4 seizures of furanylfentanyl by Customs amounting to 6.8 grams.

Germany

Germany reported 12 seizures in 2016, ranging from 1.8 to 74.3 grams. In total, approximately 200 grams of furanylfentanyl were seized. In 4 cases China was indicated as the country of origin. In the remaining seizures, the country of origin is unknown.

Luxembourg

Luxembourg reported 1 seizure of 2.9 grams seized as white powder, in a postal parcel sent from China which was destined for the Luxembourg market.

Sweden

Sweden did not provide details on the seizures. These were reported to the EMCDDA via the Swedish National Focal Point (section 3.2.2).

The level of trafficking

Information related to trafficking routes is limited to the seizures reported above. In all cases where the country of origin was known, China was indicated (Estonia, Germany, Luxembourg and Sweden).

Sweden reported that furanylfentanyl was ordered in powder form from China and then sent to Sweden, either directly or in transit via other EU Member States.

In addition, Estonia indicated that furanylfentanyl is supplied to Estonia primarily from the Czech Republic and Poland.

Additional information provided by Germany, Norway and Slovenia

Germany also reported 5 deaths associated with furanylfentanyl. These deaths occurred between February and June 2016. In 4 out of the 5 cases, post-mortem examinations confirmed that furanylfentanyl was consumed in combination with other substances.

Norway reported a death case associated with Xanax, which most likely contained furanylfentanyl. The investigation confirmed that the deceased injected 'liquid Xanax' prior to his death. The "liquid Xanax" was identified in a small bottle (Annex 2). The investigation is ongoing.

Slovenia reported a collected sample of furanylfentanyl (section 3.2.2 and Annex 2).

Additional information provided by the United States

The United States reported that no laboratories synthesising furanylfentanyl have been identified and there are no indications that the substance is produced within the country. Although there is limited information available on the substance, it appears that furanylfentanyl is produced in China, along with a variety of other fentanyl analogues, and then it is distributed to opioid users in the United States possibly facilitated by Mexican traffickers. Furanylfentanyl is distributed to opioid users mixed with or sold as heroin, or pressed into counterfeit opioid prescription pills. There is also anecdotal reporting of its availability as a nasal spray.

The producers make furanylfentanyl available for purchase online, on both the surface internet and the darknet and also through 'illicit chemical brokers'. According to a recent US Drug Enforcement Agency (US DEA) report, an illicit source-of-supply was selling a kilogram of furanylfentanyl for approximately \$5,500. The DEA has not identified any

elaborate money laundering schemes being used in furtherance of furanylfentanyl (or other fentanils) trafficking. International money remittance services are used to send funds to foreign sources-of-supply and to a lesser extent Bitcoins are used for fentanyl purchases via darkweb sites.

The US reported that furanylfentanyl has been identified in laboratory submissions across the country. Most submissions were reported in the Northeast region of the United States and were at the gram scale. A seizure of 3,500 counterfeit OxyContin tablets containing furanylfentanyl was reported in Connecticut in August 2016. In Tennessee a parcel seized in August 2016 which had originated in China contained 2.8 kg and 2.75 kg of furanylfentanyl.

According to the US National Forensic Laboratory Information System (NFLIS), which includes data from state and local laboratories, 494 samples containing furanylfentanyl were analysed as of 2 November 2016. The first NFLIS report of furanylfentanyl was in December 2015 in the State of Oregon. According to the DEA laboratory reporting system, DEA laboratories have encountered 113 samples containing furanylfentanyl as of 2 November 2016. The first submission to a DEA laboratory was in February 2016. The total number of seizures from both systems amounted to 607.

3.2.2 Information provided to the EMCDDA

The EMCDDA received responses from the 28 Member States, as well as from Turkey and Norway. Of these, 15 Member States (Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Luxembourg, Poland, Slovenia, Spain, Sweden and the United Kingdom) and Norway reported detections of furanylfentanyl⁽⁹⁾. Images of the seizures and collected samples reported to the EMCDDA are provided in Annex 1.

It is important to note that detections of furanylfentanyl may be under-reported since the substance is not routinely screened for. Two Member States (Finland and Sweden) reported that furanylfentanyl is part of routine screening. Slovenia reported that they routinely screen for furanylfentanyl in seized and collected samples.

⁽⁹⁾ 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).

Seizures

In total, 113 seizures⁽¹⁰⁾ have been reported to the EMCDDA by 12 Member States: Austria (3 seizures), Belgium (3), Cyprus (1), Denmark (1), Estonia (10), Finland (18), Germany (14), Hungary (1), Luxembourg (1), Poland (17), Sweden (38) and the United Kingdom (6). The majority of seizures were made in 2016 by Police or Customs.

The majority of furanylfentanyl seizures in Sweden were in liquid form, detected in nasal spray bottles. Most of the seizures reported by Finland were sent from Poland via airmail.

Seizures of furanylfentanyl included:

- 17 seizures of liquids in Austria, Finland and Sweden, amounting to a total of 1421 mL. Seizures in Austria and Sweden were as 'nasal spray bottles'. The largest single seizure of furanylfentanyl in liquid form was 974.5 mL seized by Police in Finland;
- 3 seizures of tablets in Sweden, amounting to 45 tablets;
- 76 seizures of powder amounting to 720.35 grams (Austria, Belgium, Cyprus, Denmark, Estonia, Finland, Germany, Hungary, Luxembourg, Sweden and the United Kingdom). The largest single seizure of furanylfentanyl in powder form was 50.08 grams seized by Estonian Customs;
- 12 seizures of herbal material amounting to 5.75 grams in Poland;
- 5 seizures of furanylfentanyl in Poland where the physical form was not reported.

Other substances detected in seized powder samples include: 4-fluoroisobutyrylfentanyl (4F-iBF); ortho-fluorofentanyl, cocaine and mannitol; diamorphine; inositol; lactose; mannitol; and paracetamol and caffeine.

No quantitative information on purity was provided.

Poland reported a case from Krakow, in 2013, regarding the production of new psychoactive substances (NPS) including the fentanils 4-fluoro-butyrylfentanyl, butyrylfentanyl and furanylfentanyl. Preliminary analysis by LC-MS/MS revealed the presence of furanylfentanyl and traces of 4-ANPP⁽¹¹⁾. NMR was not performed.

⁽¹⁰⁾ 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.

⁽¹¹⁾ 4-Anilino-*N*-phenethylpiperidine.

Collected samples

A total of 11 collected samples were reported by 3 Member States (France (4), Slovenia (1) and Spain (6)). The majority of the samples were in powder form, two samples were in liquid form, and sold as a nasal spray and as an e-liquid (France).

- the 4 samples collected by France were purchased from vendors on darknet market places: 1 of the samples was purchased as U-47700 and another sample came from China. The two samples in liquid form also contained glycerol (Annex 1).
- Slovenia reported a collected sample containing furanylfentanyl which was test-purchased from the internet (Annex 1).
- The samples reported by Spain were collected from users. The samples were sold as fentanyl (3 samples), carfentanil (1) and methadone (1).

Biological samples

A total of 20 biological samples were reported in which furanylfentanyl was analytically detected. These were reported by four Member States (Estonia, 4; Germany, 4; Sweden, 10; United Kingdom, 1) and Norway (1).

All 20 samples were taken from individuals who suffered serious adverse events (section 3.4.1).

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

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

In all cases where the origin was known, China was indicated as the country of origin (Estonia, Germany, Luxembourg and Sweden).

Estonia reported that the level of trafficking of furanylfentanyl is low after the substance was controlled nationally. Suppliers have been trying to replace fentanyl in drug market, unsuccessfully. Furanylfentanyl seized in Estonia was destined for domestic market and there is no available information on further transit and/or export.

Sweden reported that furanylfentanyl is ordered in powder form from China and then sent to Sweden, either directly or via other EU Member States. According to Swedish authorities, there are a small number of people who are involved in the trafficking of furanylfentanyl in Sweden. In

general, the same manufacturing and supply chains that deal with other fentanyl derivatives apply to furanylfentanyl.

Money laundering aspects

No information was received on money laundering in connection with the production and/or trafficking of furanylfentanyl.

Swedish authorities indicate that sales of fentanyl and fentanyl analogues via the internet generate large profits, even though the Swedish market for fentanyl is relatively limited.

Violence in connection with production, wholesale and distribution

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

Estonia reported that there is no information regarding violence related specifically to furanylfentanyl, outside what would be considered 'normal' violence associated with the trafficking of illicit drugs.

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

3.4.1 Serious adverse events reported to the EMCDDA

A total of 29 serious adverse events⁽¹²⁾ associated with furanylfentanyl were reported by four Member States (Estonia, Germany, Sweden, United Kingdom) and Norway. They comprised 10 acute intoxications and 19 deaths.

Acute intoxications

A total of 10 acute intoxications associated with furanylfentanyl were reported by three Member States (Germany, 4; Sweden, 5; United Kingdom, 1). Of these, 1 was classed as a confirmed case⁽¹³⁾, 1 as a probable case, and 8

as suspected cases⁽¹⁴⁾. They occurred between November 2015 and September 2016.

Demographics

Of the 10 intoxications, 8 were male and 2 were female. The mean age of the males was 23 (median 22) and ranged from 15 to 32 years (data available for 5 cases); the females were aged 20 and 32 years.

Substances analytically identified

Analytical confirmation was limited to the confirmed case and probable case.

In the confirmed case, furanylfentanyl, ethanol, 5-EAPB, and MDPHP were identified in the biological samples taken from the patient.

In the probable case, furanylfentanyl and mannitol were identified in a sample of the drug that was snorted by the patient.

Clinical features

The clinical features of the intoxications were generally consistent with μ -opioid agonist toxicity (data available for 7 cases). They included unconsciousness (3 cases) or reduced level of consciousness (2), respiratory arrest or depression (2) and miosis (1). In one case tachycardia and high body temperature were also reported.

It is important to note that in the confirmed case, ethanol and stimulants were also identified in the biological sample from the patient. In addition, in 2 of the suspected cases the patients reported taking either other central nervous system depressants or stimulants. Information on exposure to other substances was either unknown or not reported in the remaining 7 cases.

Administration and response to naloxone

In 3 cases⁽¹⁵⁾, naloxone was administered as an antidote. In 2 of these cases, the patients were unconscious and regained consciousness following administration of naloxone. No further details were reported in third case.

⁽¹²⁾ Serious adverse event means any adverse event, whether analytically confirmed or not, that is associated with the consumption of a new psychoactive substance in a human that: results in death; is life-threatening; requires intensive treatment in an emergency room and/or requires hospitalisation; results in persistent or significant disability or incapacity; results in substance dependency or substance abuse; consists of a congenital anomaly or birth defect; or is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are: convulsions that do not result in hospitalisation.

⁽¹³⁾ This case has been published in the literature (see Helander et al., 2016).

⁽¹⁴⁾ For the purposes of this report the following definitions are used. Confirmed case means that information on exposure to furanylfentanyl is available from analytical confirmation in one or more biological samples taken from a patient. Probable case means that information on exposure was only available from the analytical confirmation of furanylfentanyl in a drug sample and that there is a reasonable probability that the patient was exposed to that drug sample. Suspected case means that information on exposure is typically limited to the name of the substance that the patient believes that they have consumed and/or from packages containing the drugs that the patient is thought to have consumed. As a result, information on the features of the intoxication from probable and suspected cases should be interpreted with caution.

⁽¹⁵⁾ Including the confirmed case.

The information was either unknown or not reported in the remaining 7 cases.

Seriousness and outcome

In 5 cases it was reported that treatment in an emergency room/hospital was required ⁽¹⁶⁾. The information was either unknown or not reported in the remaining 5 cases.

In 5 cases the seriousness of the intoxication was classified as life-threatening (3 cases) or severe (2). In 1 case the seriousness was classed as not life-threatening. The information was either unknown or not reported in the remaining 4 cases.

In 2 cases it was reported that the patient recovered. The information was either unknown or not reported in the 8 remaining cases.

Route of administration

In 1 case a solution of furanylfentanyl was administered nasally (by nasal spray) and by intramuscular injection ⁽¹⁷⁾. In 1 case furanylfentanyl was snorted as a powder ⁽¹⁸⁾. In 2 cases furanylfentanyl was administered nasally. In 2 cases furanylfentanyl was administered orally. The information was either unknown or not reported in the 4 remaining cases.

Name of the substance/product used

In 8 cases the patient was reported to have taken 'furanylfentanyl'. The information was either unknown or not reported in the 2 remaining cases.

Source of the substance

In 2 cases furanylfentanyl was reported to have been sourced from the internet ⁽¹⁹⁾. The information was either unknown or not reported in the 8 remaining cases.

Physical form

In 3 cases the physical form of furanylfentanyl used by the patients was reported to have either been a solution in a nasal spray (2 cases) or a powder (1 case) ⁽²⁰⁾. The information was either unknown or not reported in the remaining 7 cases.

Amount or dose administered

In 2 cases ⁽²¹⁾ the amount of furanylfentanyl used was reported as 5 mg nasally (1 case) and 50 mg orally (1 case). The information was either unknown or not reported in the remaining 8 cases.

Deaths

A total of 19 deaths associated with furanylfentanyl were reported by four Member States (Estonia, 4; Germany, 4; Sweden, 9; United Kingdom, 1) and Norway (1). They occurred between November 2015 and October 2016 ⁽²²⁾.

Furanylfentanyl was analytically confirmed in biological samples from all 19 cases.

Demographics

Of the 15 deaths for which data was available, 13 were male (87%) and 2 were female (13%). The mean age of the males was 29.9 years (median 27) and ranged from 25 to 38; the two females were aged 33 and 48.

Number of deaths by year

Two deaths occurred in 2015 (November) and 17 deaths occurred in 2016 (January to October ⁽²³⁾).

Circumstances of death

In 15 cases it was reported that the decedents were found dead. This included deaths that occurred at home (6 cases) and outside (1 case). In 2 cases it was reported that drug paraphernalia and powders were found at the scene of death.

The information was either unknown or not reported in the remaining 4 cases.

Cause of death

In 12 cases the cause of death was reported. Briefly:

- In 6 cases the cause of death was reported either as overdose or intoxication with furanylfentanyl (5 cases) or intoxication with furanylfentanyl in combination with pregabalin (1 case).
- In 3 cases the cause of death was reported as overdose of narcotics (2 cases) or intoxication with drugs and narcotics (1 case).
- In 3 cases it was reported that furanylfentanyl in combination with other substances likely played a role in the death.

The cause of death was either not yet available or not reported for the remaining 7 cases.

Substances analytically identified

Information on the substances identified in biological samples was available for 18 deaths. This data was incomplete in 3 of these cases.

⁽¹⁶⁾ Including the confirmed and probable case.

⁽¹⁷⁾ The confirmed case.

⁽¹⁸⁾ The probable case.

⁽¹⁹⁾ The probable case and a suspected case.

⁽²⁰⁾ The probable case.

⁽²¹⁾ Both suspected cases.

⁽²²⁾ The month of death was not reported in one case that occurred in 2016.

⁽²³⁾ At least 16 of the deaths occurred between January and October 2016. In the remaining case that occurred in 2016 the month of death was not reported.

In 3 cases furanylfentanyl was the only substance detected; in 2 of these cases the cause of death was reported as overdose or intoxication with furanylfentanyl; in the remaining case the cause of death was not yet available.

In 15 cases other substances were detected with furanylfentanyl. In 9 cases this included other opioids (such as fentanyl in 7 cases). Other central nervous system (CNS) depressants such as benzodiazepines, ethanol, and gabapentinoids were detected in some of the deaths. In addition, THC, amphetamine, cocaine and MDMA were also detected in some cases.

Route of administration

Information on the route of administration was reported for 2 deaths. In 1 case furanylfentanyl was snorted as a powder and in 1 case it was injected intravenously. The information was either unknown or not reported in the remaining 17 cases.

Source of the substance

No information was reported on where the decedents had sourced the furanylfentanyl.

Amount or dose administered

No information was reported on the amount of furanylfentanyl administered by the decedents.

Name of the substance/product used

In 1 case the decedent was reported to have taken 'Fu-F, Furanyl-Fentanyl'. In another case furanylfentanyl may have been in a product called 'liquid Xanax' (section 3.2.1 and Annex 2). The information was either unknown or not reported in the remaining 17 cases.

3.4.2 Serious adverse events identified in open source information

In the United States, 128 deaths associated with furanylfentanyl that occurred between 2015 and July 2016 have been reported. The deaths occurred in Illinois, Maryland, New Jersey, North Carolina, and Ohio (US DEA, 2016b) ⁽²⁴⁾.

On the basis of these deaths, as well as other information, furanylfentanyl was temporarily scheduled into schedule I of the Controlled Substances Act (US DEA-DoJ, 2016).

In British Columbia, Canada, a hospital emergency department identified a large increase in suspected opioid overdose events over a four-day period in July 2016. During

this time they treated 43 patients with suspected opioid overdose. Just over 50% of the patients lost consciousness after smoking what they believed to have been crack cocaine. Samples of the drugs used by the patients were analysed and found to contain furanylfentanyl and cocaine. While most of the patients were treated and discharged within a few hours, 6 of the patients were admitted to the hospital; including 3 who were transferred to the intensive care unit, 1 of whom died (Klar et al., 2016).

3.4.3 Pharmacology

Overview

Published data on the pharmacology of furanylfentanyl are limited to *in vitro* and *in vivo* animal studies. These data suggest that furanylfentanyl is a selective and potent μ -opioid receptor agonist with a pharmacology that is broadly comparable to fentanyl.

Additional research is required in order to have a more detailed understanding of the mode and mechanism of action of furanylfentanyl and its metabolites.

Pharmacodynamics

In vitro data

Pharmacological data on furanylfentanyl have been published recently by the United States Drug Enforcement Administration (US DEA, 2016b).

The binding affinity (K_i) ⁽²⁵⁾ of furanylfentanyl to opioid receptors was evaluated using an *in vitro* preparation of transfected Chinese hamster ovary cells expressing human δ and κ opioid receptors and rat μ opioid receptors (US DEA, 2016b). Furanylfentanyl showed selectivity for the μ opioid receptor ($K_i = 0.0279 \pm 0.0080$ nM) compared to the δ ($K_i = 54 \pm 15$ nM) and κ ($K_i = 59.2 \pm 6.4$ nM) opioid receptors when [³H]-DAMGO was used as a radioligand. This experiment indicates that furanylfentanyl is a selective ligand for the μ -opioid receptor.

An *in vitro* functional assay found that furanylfentanyl ($EC_{50} = 2.52 \pm 0.46$ nM) has μ -opioid receptor agonist activity, similar to morphine ($EC_{50} = 31.0 \pm 8.2$ nM) and fentanyl ($EC_{50} = 17.9 \pm 4.3$ nM) (Table 1).

⁽²⁴⁾ In addition, a case series of 8 deaths from the United States where furanylfentanyl was analytically detected has been published (Mohr et al., 2016). This case series may be a subset of cases from the cases reported by the United States Drug Enforcement Administration (US DEA, 2016b).

⁽²⁵⁾ K_i is defined as the equilibrium dissociation constant of the ligand determined by inhibition studies.

TABLE 1

Potency of furanylfentanyl, fentanyl and morphine at the μ -, κ - and δ -opioid receptors assessed by an in vitro functional assay ([³⁵S]GTP γ S binding) measured by the EC₅₀ (nM) (US DEA, 2016).

Compound	μ -receptor	κ -receptor	δ -receptor
Furanylfentanyl	2.52 \pm 0.46	60 \pm 25	>10 μ M
Fentanyl	17.9 \pm 4.3	362 \pm 47	1190 \pm 140
Morphine	31.0 \pm 8.2	83 \pm 23	870 \pm 140

Animal studies

Furanylfentanyl was found to have analgesic activity when administered intravenously with an ED₅₀ ⁽²⁶⁾ of 0.02 mg/kg using the mouse hot plate test (Huang et al., 1986).

Comparative data for morphine and fentanyl were not reported.

Pharmacokinetics

No studies have investigated the pharmacokinetics of furanylfentanyl. Based on its structural similarity to fentanyl, it is expected to cross the blood-brain barrier, and diffuse into adipose and other tissues.

Abuse liability and dependence potential

No specific data are available on the abuse liability and dependence potential of furanylfentanyl. However, it is well documented that μ -opioid receptor agonists such as fentanyl have an abuse liability and dependence potential.

Limited information from self-reported user experiences suggests that furanylfentanyl may have an abuse liability and dependence potential.

3.4.4 Toxicology

Non-clinical data

There are no data from non-clinical studies on the acute or chronic toxicity of furanylfentanyl.

Human data

Based on the available information, it appears that poisoning with furanylfentanyl may be broadly similar to other potent fentanils and may include a rapid loss of consciousness and profound respiratory depression.

It appears that poisoning with furanylfentanyl can be reversed by administration of naloxone. Similar to poisoning with other fentanils, it has been reported that multiple doses may be required to reverse the effects (Klar et al., 2016).

⁽²⁶⁾ ED₅₀ is the dose at which 50% of test animals meet the criteria for the analgesic response.

3.4.5 Characteristics of users

Data on the characteristics of users of furanylfentanyl is limited to information provided from serious adverse events (section 3.4.1 and section 3.4.2) and self-reported user experiences from user websites.

Data from user websites should be interpreted with caution. This is because it is not possible to confirm the specific substance(s) used nor the strength, purity, dose/amount used. In addition, information provided on such sites may not necessarily be representative of other users of furanylfentanyl and should be regarded as illustrative only.

Route of administration, drug regimen

Routes of administration for furanylfentanyl includes oral (as a powder or tablet), nasal (using nasal sprays or by insufflation of a powder) and by injection (intravenous and intramuscular). These routes are similar to those reported with other fentanils. Of note is the apparent popularity of using ready-to-use or home-made nasal sprays containing solutions for the administration of furanylfentanyl. This finding extends to the use of other fentanils that have appeared in Europe in the past few years.

User websites also mention other routes of administration such as vaping solutions of furanylfentanyl using e-cigarettes. E-liquids containing furanylfentanyl have been reported by France in collected samples test-purchased from vendors on darknet marketplaces (section 3.2.2).

Poland reported several seizures of branded 'legal-high'-type products which contained furanylfentanyl in herbal material. It is not known if these products were intended to be smoked or taken orally (section 3.2.2).

User groups

The available data suggests that users of furanylfentanyl include high risk drug users and psychonauts.

Some individuals who use furanylfentanyl are polydrug users. This includes the use of other CNS depressants such as opioids, benzodiazepines, and gabapentinoids.

Settings of use

The available data suggests that one common setting of use for furanylfentanyl is the home. This finding is similar to the use of other fentanils and narcotic-analgesic opioids in general.

Dose, re-dosing, drug regimens

The available data does not allow the identification of common/typical doses of furanylfentanyl regardless of route.

There are no studies which indicate the doses required to produce subjective effects of furanylfentanyl in humans.

Subjective, psychological, and behavioural effects

There are no studies assessing the psychological and/or behavioural effects of furanylfentanyl in humans. The available data suggests that the effects of furanylfentanyl resemble those of other narcotic-analgesic opioids such as fentanyl.

Effect on ability to operate machinery and drive

Based on the available data it should be assumed that the acute behavioural effects of furanylfentanyl on operating machinery and driving are similar to those caused by other opioid narcotic-analgesics such as fentanyl. This includes the potential for profound CNS depression.

Availability, supply, price

Online vendors

A structured search by the EMCDDA of online vendors ⁽²⁷⁾ of furanylfentanyl on the surface web ⁽²⁸⁾ was conducted in December 2016. The search identified 46 vendors that appeared to be based in, and/or claim to have presence in China (n = 27 sites), the United States (n = 5 sites), Hong Kong (n = 3 sites), India (n = 1 site), South Korea (n = 1 site), Ukraine (n = 1 site) and the United Kingdom (n = 1 site). For the remaining 7 vendors, there was no apparent location mentioned.

Twenty two of the sites provided quantities and prices for furanylfentanyl upon request. The remaining 24 sites listed quantities and prices. In brief:

- Furanylfentanyl was usually offered in powder form. Typically it was listed as a 'research chemical, not fit for human consumption';
- One site offered furanylfentanyl as a ready-to-use nasal spray and also 'o-liquid' intended for vaping in e-cigarettes. This site also offered furanylfentanyl in powder form mixed with either mannitol (ratio of 1:10) or caffeine (ratio of 1:25);
- The minimum quantity offered was 1 g (n = 6 sites) with a mean price of EUR 54;
- The mean price for 10 g was EUR 193 (n = 6 sites), 100 g was EUR 924 (n = 5 sites) and 1 kg EUR 5299 (n = 4 sites);
- The maximum quantity offered was 5 kg with a price of EUR 29,467 (n = 1 site).

⁽²⁷⁾ This includes vendors that appear to be consumer-orientated as well as vendors which appear to be manufacturers and/or wholesalers (for example on B2B sites). It excludes those selling furanylfentanyl through online classified advertisements, social media, and user websites.

⁽²⁸⁾ The search of online vendors of furanylfentanyl was performed on 19/12/2016 using the search strings: 'buy furanylfentanyl' (searches in English, Swedish and Danish, including variations in spelling). The first 100 results were recorded and the sites reviewed. Each identified vendor site was then scored for information on geographical location, quantities and prices, and substance marketing.

Prices were listed in United States Dollars on all 24 sites ⁽²⁹⁾.

In 4 collected samples reported by France, the furanylfentanyl was purchased from vendors on darknet marketplaces.

Prevalence of use

No general population surveys or targeted surveys were identified that had examined the prevalence of use of furanylfentanyl.

In addition, it is possible that some users may not be aware that they are taking furanylfentanyl. In Europe, furanylfentanyl has been sold as other opioids (including methadone). It has also been detected with heroin in one small seizure. In addition, it has also been detected in branded legal high products. In Canada, furanylfentanyl in crack cocaine was responsible for an outbreak of serious poisonings during July 2016. Users who are unaware that they are taking furanylfentanyl could be at increased risk of serious poisoning.

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

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

On 23 November 2016, the World Health Organization informed the EMCDDA that furanylfentanyl is currently not under assessment and has not been under assessment by the UN system.

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

The first official EMCDDA–Europol notification of furanylfentanyl dates from 3 November 2015 from the Finnish National Focal Point. The Reporting Form details the seizure of furanylfentanyl in 0.2 grams of pale brown powder in incoming mail from Poland, seized by Finnish Customs on 29 June

⁽²⁹⁾ Prices listed in USD were converted to EUR according to the XE Currency Converter from the 11/01/2017 (USD 1 = EUR 0.95). The prices were then rounded up to the nearest EUR.

2015. The identification and analytical characterisation by GC-MS, LC-MS and NMR was conducted by the Swedish National Forensic Centre.

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

It is important to note that it appears that furanylfentanyl was first detected in 2013, as evidenced by the report of a detection of furanylfentanyl in a sample seized during a case involving the production of NPS in Poland (section 3.2.2). However, it appears that, where known, furanylfentanyl has been sourced outside the EU.

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

Seven Member States (Cyprus, Denmark, Estonia, Finland, Latvia, Lithuania and the United Kingdom) and Turkey reported that furanylfentanyl is controlled under drug control legislation.

- In Cyprus, furanylfentanyl is controlled within the context of a generic clause which addresses fentanyl chemical groups.
- In Denmark, it is included in the amendment of the Executive Order on Euphoriant Substances which entered into force on 24 November 2016.
- In Estonia furanylfentanyl is controlled by way of generic definition.
- In Finland, the substance is controlled as a narcotic since 1 April 2016.
- In Latvia, furanylfentanyl 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'.
- In Lithuania, furanylfentanyl is subjected to control measures by The Republic of Lithuania Minister of Health Order No V-1511 (28/12/2015) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000'.

- In the United Kingdom, furanylfentanyl is controlled under the Misuse of Drugs Act 1971 by way of a generic definition.
- In Turkey, furanylfentanyl is under control of Drug Law on Drugs numbered 2313 (Official Gazette 29790 of 3 August 2016).

Three Member States (Austria, Hungary and Poland) reported that furanylfentanyl is controlled under specific new psychoactive substances control legislation.

- In Austria, furanylfentanyl is covered by the Austrian Act on New Psychoactive substances.
- In Hungary, furanylfentanyl is listed in the ministerial decree No. 55/2014 (XII.3.) EMMI since 25 December 2016.
- In Poland, furanylfentanyl is controlled according to the general definition of the 'substitute drug'. Pursuant to Article 44b of the Act on counteracting drug addiction and Article 27c of the Act of 14 March 1985 on State Sanitary Inspection (Journal of Laws 'Dz. U.' of 2011, No. 212, item 1263), it is prohibited to manufacture and introduce substitute drugs to trade.

Germany reported that it is not known whether furanylfentanyl may be controlled under specific NPS control legislation ⁽³⁰⁾.

One Member State (Sweden) and Norway reported that furanylfentanyl is controlled under other types of legislation:

- In Sweden, furanylfentanyl is regulated in the Act on the Prohibition of Certain Goods Dangerous to Health (SFS 1999:42), as of 26 January 2016.
- In Norway, the import of and trade in furanylfentanyl is controlled by the Medicinal Products Legislation.

Sixteen Member States (Belgium, Bulgaria, Croatia, Czech Republic ⁽³¹⁾, France, Greece, Ireland, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia ⁽³²⁾ and Spain) reported that furanylfentanyl is not subject to control measures at the national level.

⁽³⁰⁾ The substance was discussed in the bi-annual expert committee in December 2016 but no official decision had been published at the time of writing the report.

⁽³¹⁾ The Czech Republic reported that it has been proposed that the substance is included in the amendment of Government Regulation No. 463/2013 Coll. It is expected that the amendment will come into force in early 2017.

⁽³²⁾ Slovenia reported that the proposal for regulation of furanylfentanyl is in the legislative procedure.

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

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

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

The synthesis of furanylfentanyl was first described in a 1986 patent (Huang et al., 1986). The published synthetic method for furanylfentanyl describes the addition of 2-furoyl chloride to the precursor 4-ANPP^(33,34).

The detection of traces of 4-ANPP in a seized sample of furanylfentanyl in Poland and the availability of 4-ANPP on the chemicals market suggest it may have been used as a precursor in the manufacture of furanylfentanyl. The seized furanylfentanyl sample was from a case in Krakow that involved the production of a number of different new psychoactive substances. Two other fentanyl derivatives, 4-fluoro-butyrfentanyl and butyrfentanyl, were also detected during analysis of seized samples from this case.

The manufacture of furanylfentanyl relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl (Casy and Huckstep, 1988; Gupta et al., 2013; Zee and Wang, 1980). Therefore the methods developed for the synthesis of fentanyl are applicable to the synthesis of furanylfentanyl.

Most of the synthetic procedures are straightforward, use common laboratory equipment and precursors, and detailed recipes are available on the internet⁽³⁵⁾. While only basic knowledge of synthetic chemistry is required, due to the potency of fentanils extreme caution is required when carrying out the final synthetic step as well as when purifying and handling the substance⁽³⁶⁾. Exposure of the skin and mucous membranes to fentanils as well as their inhalation pose

⁽³³⁾ CAS RN: 21409-26-7. For analytical characterisation, see: <http://www.swgdrug.org/Monographs/4ANPP.pdf>. Note that 1-(2-phenylethyl)piperidin-4-one, or NPP (CAS RN: 39742-60-4), a precursor to 4-ANPP, is also used for the manufacture of the bronchodilatory medicine fenspiride.

⁽³⁴⁾ The synthesis of 4-ANPP from phenethylamine and ethyl (or methyl) acrylate is well documented (Beckett et al., 1959; Jończyk et al., 1978; Maryanoff et al., 1982). For another route, see Valdez et al., 2014.

⁽³⁵⁾ 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>).

⁽³⁶⁾ Self-educated clandestine chemists commented on the risk while discussing the synthesis of fentanyl and its potent 3-methyl and α -methyl homologues (comment was posted on 7 May, 2002); available at: <https://the-hive.archive.erowid.org/forum/showflat.pl?Cat=&Number=260275> (Accessed: 6 October 2016).

a serious risk of accidental poisoning. In addition to exercising extreme caution, suitable personal protective equipment as well as sufficient stocks of naloxone as an antidote to poisoning following accidental exposure should be available when handling materials suspected to contain these substances (CDCP, 2013; US DEA, 2016a).

The precursors *N*-phenethyl-4-piperidone (NPP) and 4-ANPP are offered from gram to bulk (multikilogram) quantities on the internet from dozens of suppliers. For example, prices for the immediate precursor 4-ANPP range from USD 75 per 100 gram to USD 5000 per 1 kg.

Neither NPP nor 4-ANPP are included in Table I or Table II of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988. In June 2010, the US Drug Enforcement Administration placed 4-ANPP (named ANPP in the regulation) into Schedule II of the Controlled Substances Act (US DEA-DoJ, 2010).

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

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

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

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

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

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

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

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

Nine countries (Austria, Denmark, Finland, France, Greece, Latvia, Poland, Slovakia and Spain) provided information that furanylfentanyl is not used to manufacture a medicinal product for veterinary use. Eleven countries (Belgium, Estonia, Germany, Hungary, Iceland, Ireland, the Netherlands, Norway, Portugal, Slovenia and Sweden) reported that it was unknown if furanylfentanyl is used to manufacture a medicinal product for veterinary use.

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

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

4.1 Marketing authorization

Twenty countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, the Netherlands, Norway, Slovakia, Spain, Sweden and the United Kingdom) reported that furanylfentanyl has not been granted a marketing authorization as a medicinal product for human use.

Twenty countries (Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain and Sweden) reported that furanylfentanyl has not been granted a marketing authorization as a medicinal product for veterinary use.

The EMA also reported that furanylfentanyl has not been granted a marketing authorization as a medicinal product for

neither human nor veterinary use through the centralized procedure.

4.2 Application for a marketing authorization

Twenty countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, the Netherlands, Norway, Slovakia, Spain, Sweden and the United Kingdom) reported that furanylfentanyl is not the subject of an application for a marketing authorization as a medicinal product for human use.

Twenty countries (Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain and Sweden) reported that furanylfentanyl is not the subject of an application for a marketing authorization as a medicinal product for veterinary use.

The EMA also reported that furanylfentanyl is not the subject of an application for a marketing authorization for neither human nor veterinary use through the centralized procedure.

4.3 Suspended marketing authorization

Twenty countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, the Netherlands, Norway, Slovakia, Spain, Sweden and the United Kingdom) reported that there had been no cases of suspended marketing authorization in respect to furanylfentanyl as a human medicine.

Twenty countries (Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain and Sweden) reported that there had been no cases of suspended marketing authorization in respect to furanylfentanyl as a veterinary medicine.

The EMA also reported that furanylfentanyl is not the subject of a suspended marketing authorization for neither human nor veterinary use through the centralized procedure.

5. Conclusion

Furanylfentanyl is a synthetic opioid. It is closely related to fentanyl, which is controlled under the United Nations Single Convention on Narcotic Drugs of 1961. Data suggests that furanylfentanyl is likely to be a potent opioid narcotic analgesic and may have an abuse liability and dependence potential in humans; these effects may be broadly comparable to fentanyl.

Furanylfentanyl has been available in the European Union since at least June 2015 and has been detected in 16 Member States and Norway. In most cases it has been seized as a powder, but other forms such as liquids, tablets, and herbal material have also been detected. The detected quantities are relatively small; however, they should be seen within the context of the high potency of the substance.

There are indications that the furanylfentanyl currently available on the market is synthesised by chemical companies based in China. Furanylfentanyl is sold online often under the guise of a 'research chemical'. It is available in wholesale amounts up to 5 kilograms and in consumer amounts. In the latter case, these include ready-to-use nasal sprays. There is one report that indicates that furanylfentanyl was synthesised in a clandestine laboratory in Europe in 2013.

Nineteen deaths associated with furanylfentanyl have been reported by 4 Member States and Norway, all of which were analytically confirmed. 90% of the deaths occurred during 2016. In at least 9 of the deaths furanylfentanyl was the cause of death or contributed to the death.

Information on the use of furanylfentanyl in Europe is limited. It appears that furanylfentanyl is used as a drug in its own right. However, serious concerns exist that the substance could be supplied surreptitiously to a range of drug users, including those who inject opioids.

Furanylfentanyl is not currently under assessment and has not been under assessment by the UN system. Furanylfentanyl is not subject to control measures in 16 Member States.

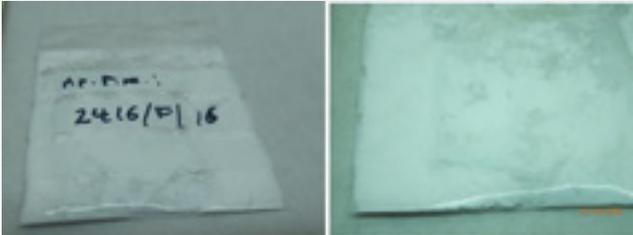
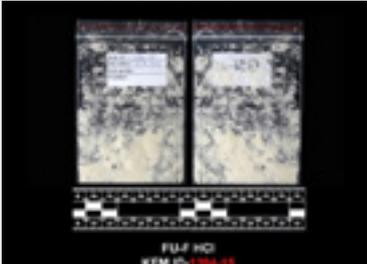
We conclude that the health and social risks caused by the manufacture, trafficking and use of furanylfentanyl, and the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure in accordance with Article 6 of Council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

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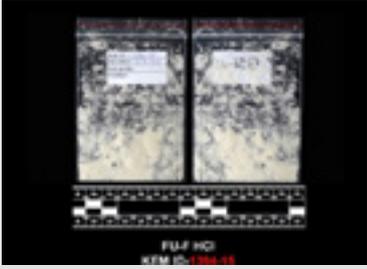
Annex 1

Images from seizures and collected samples provided to the EMCDDA

Country	Image	Description
Cyprus		<p>Seizure Date: 19 August 2016 White powder, 0,87 grams Seizing authority: Police at Limassol</p>
France		<p>Collected sample Date: 14 October 2016 Nasal spray Collecting authority: OFDT, SINTES – test purchase</p>
France		<p>Collected sample Date: 17 October 2016 E-liquid Collecting authority: OFDT, SINTES – test purchase</p>
Slovenia		<p>Collected sample Date: 12 December 2017 Off-white powder Collecting authority: Slovenian National Forensic Laboratory – test purchase in the frame of EU co-funded project RESPONSE</p>

Annex 2

Images provided to Europol

Country	Image	Description
Czech Republic		<p>Seizure Plastic zip lock</p>
Slovenia		<p>Collected sample Collecting authority: Slovenian National Forensic Laboratory – test purchase in the frame of EU co-funded project RESPONSE</p>
Norway		<p>Seizure recovered from a scene of death 'Liquid Xanax' 'Most likely contained furanylfentanyl'</p>

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

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