



Furanylfentanyl

Report on the risk assessment of *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) in the framework of the Council Decision on new psychoactive substances

About this series

EMCDDA Risk Assessments are publications examining the health and social risks of individual new psychoactive substances.

The Risk Assessment Report consists of an analysis of the scientific and law enforcement information available on the new psychoactive substance under scrutiny and the implications of placing it under control. It is the outcome of a meeting convened under the auspices of the EMCDDA Scientific Committee.

This process is part of a three-step procedure involving information exchange/early warning, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

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Foreword

This publication presents the data and findings of the risk assessment on furanylfentanyl (*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide), carried out by the extended Scientific Committee of the EMCDDA on 23 May 2017.

The Risk Assessment Report, which was submitted to the European Commission and the Council of the European Union on 23 May 2017, examines the health and social risks of the drug, information on international trafficking and the involvement of organised crime, as well as a consideration of the potential implications of subjecting the drug to control measures. Furanylfentanyl is the fourteenth new psychoactive substance to be risk assessed under the terms of Council Decision 2005/387/JHA.

On the basis of the Risk Assessment Report — and on the initiative of the European Commission — on 15 November 2017, the Council decided that furanylfentanyl should be subject to control measures across the Member States. This decision was adopted in the final stage of the three-step process — early warning, risk assessment and control of new psychoactive substances — established by the Council Decision 2005/387/JHA. This legal framework allows the EU institutions and Member States to act on all new and potentially threatening narcotic and psychotropic drugs which appear on the European drug scene, with the EMCDDA and Europol, in collaboration with their respective networks playing a central role in the early detection of such substances as well as the harms caused by their use — information that underpins risk assessment, and, ultimately, decision-making.

In this respect we would like to acknowledge the excellent work done by the networks of the EMCDDA and Europol, as well as those of the EMA — the Reitox national focal points, Europol national units and the national competent authorities responsible for medicinal products — who played an essential role in collecting and providing national data.

Finally, we would like to thank all the participants in the risk assessment process for the high quality of work carried out. The resulting report is a valuable contribution at European level, which gives clear support to political decision-making.

Professor Dr Gerhard Bühringer

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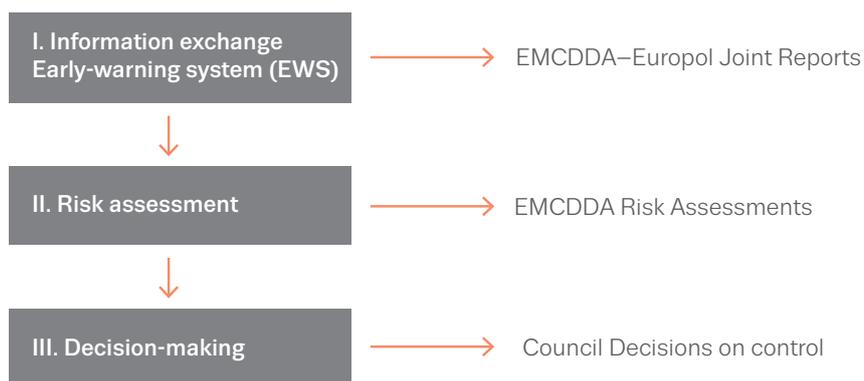
EMCDDA actions on monitoring and responding to new drugs

The EMCDDA has been assigned a key role in the detection and assessment of new drugs in the European Union under the terms of a Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances.

It establishes a mechanism for the rapid exchange of information on new psychoactive substances and provides for an assessment of the risks associated with them in order to permit the measures applicable in the Member States for the control of narcotic and psychotropic substances to be applied also to new psychoactive substances.

The three-step process involves information exchange/early warning, risk assessment and decision-making (see below). More detailed information can be found in the section 'Action on new drugs' of the EMCDDA's website: www.emcdda.europa.eu/activities/action-on-new-drugs

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances:



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

Europol–EMCDDA Joint Report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]-furan-2-carboxamide — in accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

In November 2016, the EMCDDA and Europol examined the available information on a new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]-furan-2-carboxamide, commonly known by the abbreviation '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 available on furanylfentanyl satisfied criteria 4 and 6. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report on furanylfentanyl as stipulated by Article 5.1 of the Decision. Accordingly, the NFPs, the Europol national units (ENUs), the EMA and the World Health Organization (WHO) were formally asked to provide the relevant information within six weeks from the date of the request, i.e. by 28 December 2016.

The resulting Joint Report on furanylfentanyl was submitted to the Council, the Commission and the EMA on 23 January 2017. The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in furanylfentanyl, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA.

The full text of the Joint Report can be found at:
www.emcdda.europa.eu/publications/joint-reports/furanylfentanyl

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

Introduction

This Risk Assessment Report presents the summary findings and the conclusion of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (commonly known as furanylfentanyl). 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 furanylfentanyl, 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⁾.

Furanylfentanyl was formally notified on 3 November 2015 by the EMCDDA on behalf of the Finnish national focal point, in accordance with Article 4 of the Council Decision. The notification related to the seizure of 0.2 g of powder seized on 29 June 2015 by customs in incoming mail from Poland. Following an assessment of the available information on furanylfentanyl, and in accordance with Article 5 of the Council Decision, on 23 January 2017 the EMCDDA and Europol submitted a

⁽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.

⁽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.

Joint Report on furanylfentanyl ⁽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 28 February 2017, 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 furanylfentanyl was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of two 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 furanylfentanyl, 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 23 May 2017 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 (page 47).

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

- Technical report on *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) (Annex 1);
- EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) ⁽⁶⁾;
- Open source information including scientific articles, official reports, grey literature, internet drug discussion forums and related websites (hereafter 'user websites');
- An unpublished *in vivo* pharmacology study kindly provided by the United States Drug Enforcement Administration ⁽⁷⁾;
- Additional information provided during the course of the risk assessment meeting by the participants;
- The EMCDDA operating guidelines for the risk assessment of new psychoactive substances ⁽¹⁾; and,
- Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ⁽²⁾.

Finally, it is important to note that this Risk Assessment Report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with furanylfentanyl. 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.

Physical, chemical and pharmacological description

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) is a furan-2-carboxamide derivative of *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine and structurally related to fentanyl, which is a propionamide (Figure 1). Furanylfentanyl contains one basic nitrogen atom in the piperidine ring readily forming salts with organic or inorganic acids ⁽⁸⁾. Fentanyl analogues (fentanils), have in common an aralkyl group attached to a 4-*N*-acylanilino-piperidine.

Furanylfentanyl is known from the scientific literature. Fentanyl is a fast but short-acting synthetic opioid that has been widely used in clinical practice including as an

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

⁽⁷⁾ Contract No. 224-16-050R.

⁽⁸⁾ Note that although 'furanylfentanyl' can refer to 2- and to 3-furanylfentanyl, in this report it will reference the 2- isomer

adjunct to general anaesthesia during surgery and for postoperative pain management. Furanylfentanyl is also structurally related to acetylfentanyl and acrylolylfentanyl (Figure 1), both of which were the subject of an EMCDDA–Europol Joint Report in December 2015 and December 2016 following more than 30 deaths and more than 40 deaths, respectively.

Pharmacologically, furanylfentanyl is an opioid receptor agonist.

Synthetic opioids like fentanyl and related 4-anilinopiperidine derivatives are potent analgesics. Initially developed in the 1960's as part of research efforts to develop safer and better opioid analgesics, a small number of this family of compounds — alfentanil, fentanyl, sufentanil and remifentanyl — have become widely used in human medicine as adjuncts to general anaesthesia during surgery and for pain management. They are available in a wide variety of formulations, such as liquids for injection, tablets, transdermal patches, lozenges and nasal sprays. Some are also used in veterinary medicine as general anaesthetics, for pain

management, and, in the case of carfentanil and thiafentanil, to immobilise large animals.

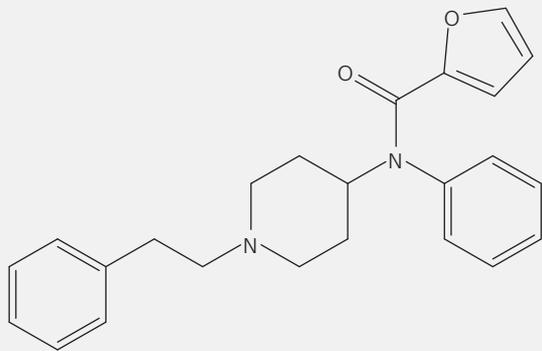
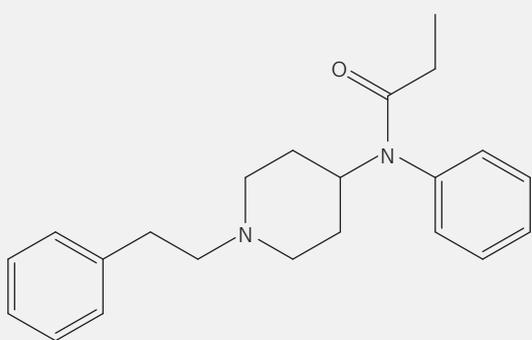
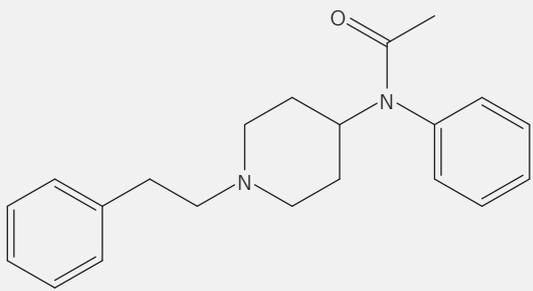
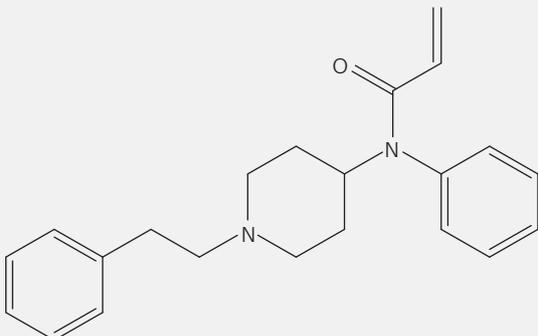
Fentanyl analogues first emerged on the illicit drug market in the United States of America in 1979. At the time they were not controlled under drug legislation. They were manufactured in clandestine laboratories and sold on the heroin market as heroin or 'synthetic heroin'.

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

The major pharmacological effects of the fentanils, including their analgesic activity, are due to their activation of opioid receptors, and, in particular, the μ -opioid receptor. Besides their analgesic properties, a notable feature associated with μ -opioid receptor agonists is that they cause dose-dependent respiratory depression, in which overdose can be life-threatening. Other additional pharmacological effects include miosis, sedation, bradycardia, hypothermia, constipation, physical dependence, and changes in mood such as euphoria.

FIGURE 1

The molecular structure, molecular formula and molecular mass of furanylfentanyl compared to fentanyl, acetylfentanyl, and acrylolylfentanyl.

	
Furanylfentanyl	Fentanyl
$C_{24}H_{26}N_2O_2$	$C_{22}H_{28}N_2O$
374.48 g/mol	336.48 g/mol
	
Acetylfentanyl	Acrylolylfentanyl
$C_{21}H_{26}N_2O$	$C_{22}H_{26}N_2O$
322.44 g/mol	334.46 g/mol

Furanylfentanyl as free base or as its hydrochloride salt may occur as solids. There is no solubility data on furanylfentanyl or its hydrochloride salt; however due to its close similarity to fentanyl, the free base is expected to be poorly soluble in water and highly lipophilic.

In Europe, furanylfentanyl has been seized as powder and in liquid solutions. In the latter case this includes nasal sprays. To a lesser extent, it has also been seized as tablets and in green 'herbal' material. It has also been sold as e-liquids for vaping in electronic cigarettes.

The analytical identification of furanylfentanyl in physical and biological samples is possible using several analytical techniques. Analytical data have been described using GC-MS, FTIR-ATR, GC-sIR, HPLC-TOF-MS, LC-QTOF-MS, LC-MS/MS, TD-DART-MS, IMS, IC, ¹H and ¹³C NMR.

The availability of analytical reference material is important for correct identification and for facilitating the quantification of furanylfentanyl in physical and biological samples; such reference materials are now commercially available. It should be noted that concentrations in blood samples can be in the sub-nanogram per millilitre range.

As furanylfentanyl has only been on the drug market for a short period of time it may not be part of most drug screenings and therefore may be undetected and/or under-reported.

Route of administration and dosage

Furanylfentanyl 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 vaporising; and, administered transdermally by injection (intravenous and intramuscular). Furanylfentanyl has also been offered for sale in the form of propylene glycol/glycerol solutions (e.g. 30 mg/mL), presumably intended for vaporisation as an e-liquid in electronic cigarettes ('vaping'). Discussions on user websites include the descriptions of blotters.

In the acute intoxications suspected to involve furanylfentanyl that were reported to the EMCDDA, the routes of administration were: nasally (using a nasal spray), by intramuscular injection, snorted as a powder, inhaled or administered orally.

In the deaths associated with furanylfentanyl, the routes of administration included intravenous injection, snorting, and mixed routes of oral and injection.

From the limited data available it is not possible to discern the 'typical' dosages administered by users. While a range of doses have been reported, 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.

Analysis of the concentration of nasal spray solutions of furanylfentanyl seized in Finland found that they contain between 1.1 and 3.2 mg/mL of the substance.

Doses reported on user websites range from 0.3 to 1.6 mg (oral administration) and from 0.2 to 0.8 mg and above (insufflation). The assessment of such reports is problematic not least because the purity, amount and/or composition of the substance ingested are typically not known by the user. Moreover, the actual composition of the substance may differ over time and different geographical areas.

Pharmacology

Pharmacodynamics

Currently available data on the pharmacology of furanylfentanyl are limited to studies investigating its binding and functional activity at opioid receptors *in vitro*, and its antinociceptive properties in mice. Briefly, these data show that furanylfentanyl is a μ -opioid receptor agonist with antinociceptive properties similar to fentanyl.

Data from *in vitro* binding studies suggest that furanylfentanyl binds to the μ -opioid receptor (MOR) with high selectivity over the κ - (KOR) and δ -opioid receptors (DOR). Furanylfentanyl shows higher binding affinity than morphine (at MOR and DOR) and fentanyl (at MOR, KOR and DOR). Data from *in vitro* functional studies suggest, however, that furanylfentanyl functions as an agonist with lower functional efficacy when compared to morphine and fentanyl.

Data from studies in mice examining the antinociceptive properties of furanylfentanyl found that when administered intravenously, the substance reduces the response to pain experimentally induced by heat. This effect may be broadly comparable to those of fentanyl but more potent than for morphine. The antinociceptive

effects of furanylfentanyl were reversed by the opioid antagonist naltrexone.

Pharmacokinetics

Studies on the pharmacokinetics of furanylfentanyl are limited to the identification of metabolites. Due to its lipophilicity, furanylfentanyl, like fentanyl, is expected to readily cross the blood-brain barrier and also diffuse into fat and other tissues and is thus likely to have a large volume of distribution.

The pharmacokinetics and the metabolic pathway of furanylfentanyl are expected to share some similarities with other fentanils. As such, furanylfentanyl could be predicted to undergo metabolism by hepatic CYP450 isoenzymes, including CYP2C19, CYP2D6, CYP3A4, and CYP3A5.

A recent study using human post-mortem urine samples suggested the identification of nine metabolites including 4-ANPP. While 4-ANPP might also be present as a synthesis by-product, this substance does exert some biological activity, although at several orders of magnitude lower than morphine. Further studies are required to assess the metabolism of furanylfentanyl and whether the other metabolites exert biological activity of pharmacological and toxicological relevance.

Inter-individual genetic variability in metabolising enzymes

There is no information on the inter-individual genetic variability in metabolising enzymes for furanylfentanyl. For fentanyl, oxidative dealkylation by hepatic CYP3A4 and by CYP3A5 isoenzymes to norfentanyl has been demonstrated. The variation of the expression of the genes coding for these CYP3A isoenzymes among populations might be of clinical significance but further studies are needed to address the toxicological consequences of such polymorphisms.

Interactions with other substances, medicines, and other forms of interactions

While specific information about furanylfentanyl could not be identified it is conceivable that interactions observed with fentanyl and other opioid narcotic analgesics might apply.

For example, should furanylfentanyl be metabolised by CYP450 3A4 and CYP450 3A5 isoenzymes, then the use

of this substance with strong or moderate inhibitors of these isoenzymes (such as clarithromycin, erythromycin, fluconazole, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, ritonavir, saquinavir, suboxone, verapamil) may result in increased plasma concentration of furanylfentanyl which could be toxicologically significant. Overall, this could increase the risk of poisoning including potentially fatal respiratory depression.

The concomitant use of other central nervous system (CNS) depressants with opioid analgesics, including other opioids, sedatives/hypnotics (such as the benzodiazepines and the z-drugs), ethanol (alcohol), gabapentinoids (pregabalin and gabapentin), tranquillisers, sedating anti-histamines, and skeletal muscle relaxants may produce additive depressant effects. Of note in this respect is that polydrug use was common in the deaths reported to the EMCDDA, including the use of other CNS depressants such as benzodiazepines, pregabalin, gabapentin and ethanol.

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 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 is also seen with furanylfentanyl.

Similar to fentanyl, the use of partial opioid agonists/antagonists (such as buprenorphine, nalbuphine, pentazocine) which have high affinity to opioid receptors but relatively low intrinsic activity could partially antagonise the effects of furanylfentanyl and may induce withdrawal symptoms in people who are opioid dependent. It is unknown if such effects are possibly protective in individuals poisoned with furanylfentanyl or other fentanils.

Psychological and behavioural effects

From the available data, it appears that the psychoactivity of furanylfentanyl is similar to that of other opioid analgesics which includes relaxation and euphoria; at higher doses, profound intoxication can be expected.

Legitimate uses

Furanylfentanyl has no established or acknowledged medical value or use (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for furanylfentanyl in

the European Union nor in the Member States that responded to the information request from the European Medicines Agency (EMA) that was launched under Article 5 of the Council Decision. In addition, there is no information to suggest furanylfentanyl is used for the manufacture of a medicinal product or an active pharmaceutical ingredient (API) of a medicinal product in the European Union. It should be noted that there is no European Union database on the synthetic routes of all registered medicinal products.

Furanylfentanyl is used as an analytical reference standard and for use in scientific research. There are no reported uses of furanylfentanyl as a component in industrial, cosmetic or agricultural products.

Chemical precursors that are used for the manufacture

Information on the chemical precursors and the synthetic methods employed for furanylfentanyl detected on the drug market within the European Union is limited. Impurities detected in a sample collected from a test purchase from an Internet vendor suggest the presence of furan-2-carboxylic acid, which would be consistent with hydrolysed reagents used in the acylation step. In addition, two countries reported powdered samples containing 'synthesis by-products' although these were not specified.

The manufacture of furanylfentanyl most likely relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl. Accordingly, methods developed for the synthesis of fentanyl are applicable to furanylfentanyl. Most of these are straightforward, make use of common laboratory equipment and precursors, and require only basic knowledge of chemistry. A one-step method uses 4-ANPP and furanoyl chloride for the manufacture of the substance. Use of a different acylating agent in the final acylation step could provide other fentanils.

Two potential precursors of fentanyl and other fentanils, *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) as well as *N*-phenethyl-4-piperidone (NPP, a pre-precursor), have been recently scheduled ⁽⁹⁾.

Due to the high potency of furanylfentanyl there is a serious risk of severe poisoning following accidental

exposure during its manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substance.

Health risks

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of furanylfentanyl, 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 acute intoxications and deaths reported to the EMCDDA as well as information from user websites, that individuals may have used other substances in addition to furanylfentanyl. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the reported effects.

Furanylfentanyl is available as ready-to-use nasal sprays which typically contain milligram amounts of dissolved substance. The preparation of solutions containing milligram amounts of substance 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, which are unlikely to be able to control the exact dose of furanylfentanyl being consumed.

While specific information for furanylfentanyl is limited, recent seizures in Europe of nasal sprays containing other fentanils revealed 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 serious risk of poisoning.

Furanylfentanyl may be used in combination with other drugs (intentionally or unintentionally).

Limited data from seizures and collected samples have shown that furanylfentanyl has been detected in mixtures containing other opioids such as heroin, U-47,700, fentanyl, 2-fluorofentanyl, 4-fluoroisobutyrylfentanyl and carfentanyl; as well as cocaine, caffeine, paracetamol, and sugars/sugar alcohols (lactose, mannitol, inositol). The

⁽⁹⁾ Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988

overall significance of these seizures is unclear; however, the identification of carfentanil is of serious concern given its potency. In addition, the identification of heroin and fentanyl in the seizures suggests that furanylfentanyl is being supplied through the illicit heroin/opioid market.

Acute toxicity

No studies were identified that have investigated the acute effects of furanylfentanyl and/or its metabolites in animal or humans. For fentanyl the estimated lethal dose in humans could be as low as 2 mg by intravenous injection.

Although *in vitro* studies have established that furanylfentanyl is a potent agonist of the μ -opioid receptor, it is not known whether this effect, which is also responsible for respiratory depression (among other physiological effects), would translate to high toxicity in humans.

Acute intoxications

Eleven acute intoxications associated with furanylfentanyl were reported by three countries: Germany (4 cases), Sweden (5), and the United Kingdom (2). Only 1 case was analytically confirmed from biological samples taken from the patient, with the remaining cases either being probable (1 case) or suspected cases (9). They occurred between November 2015 and September 2016. The majority of these cases related to acute poisoning presentations to hospital emergency departments that were reported to poison centres.

Where known, furanylfentanyl was administered intranasally using a nasal spray or snorted as a powder or taken orally. In one case a nasal solution was injected intramuscularly.

Of the acute intoxications, 9 were male and 2 were female. The mean age of the male cases for which an age was known was 23 (median 22) and ranged from 15 to 32 years (data available for 5 cases); the female cases were aged 20 and 32 years. At least 6 cases required treatment in hospital. Three cases were classed by the poison centres as life-threatening or severe and one was classed as not life-threatening. The information was either unknown or not reported in the remaining 7 cases.

Use of the antidote naloxone was reported in 4 of the cases, with apparent reversal of the poisoning reported in 3 of these cases.

In 2 cases it was reported that the patient recovered; in the remaining 9 cases the outcome was unknown.

Reported clinical features included: miosis, unconsciousness, and respiratory depression; however, the lack of analytically confirmed drugs in the majority of cases hinders the interpretation of this as other drugs may have caused or contributed to the features observed. Nevertheless, such clinical features would be consistent with poisoning from an opioid, including fentanils.

Recently, a group of cocaine users in Canada were treated for opioid overdose symptoms in a hospital emergency department after they had smoked what they believed to have been crack cocaine. Analysis of samples of the drug used by the patients identified furanylfentanyl and cocaine in a mixture. Of particular note is that community members, first responders, and emergency department staff reported that patients required high doses of naloxone, in some cases up to 3.0 mg.

Deaths

Twenty-three deaths associated with furanylfentanyl were reported by six countries: Estonia (4 deaths), Finland (1), Germany (4), Sweden (12), United Kingdom (1), and Norway (1). In all cases, furanylfentanyl was analytically confirmed from post-mortem samples.

Where known, 17 of the cases were male and 2 cases were female. The mean age of the males was 32.9 years (median 32) and ranged between 25 and 53 years; the age of the females were 33 and 48 years.

All the deaths occurred between November 2015 and February 2017; two deaths occurred in 2015, 19 in 2016 and 2 in 2017.

Circumstantial information, as well as analysis of hair samples, suggests that that some of decedents were high-risk drug users, including opioid users.

Cause of death and toxicological significance

In 10 of the 23 deaths, furanylfentanyl was reported to be the cause of death or to have contributed to death; in 2 of these deaths furanylfentanyl was the sole drug present. In 3 deaths furanylfentanyl was assumed to have contributed to death. In 3 cases the cause of death was reported as an 'overdose with drugs or narcotics', with no substances explicitly mentioned. In the remaining 7 cases the cause of death had not yet been established, was not known, or was not reported.

A range of other substances were found in the deaths, including: benzodiazepines, gabapentinoids (pregabalin, gabapentin), ethanol, THC, amphetamine, MDMA, cocaine, antidepressants and antipsychotics. In 11 cases, furanylfentanyl was the sole opioid present. In the remaining 12 cases, other opioids detected were: fentanyl (6 deaths), acetylfentanyl (2), buprenorphine (2), tilidine (2), methadone (1), 4-chloroisobutyrylfentanyl (1), and tramadol (1).

No information was available regarding symptoms experienced by the decedents prior to death.

Sufficient data was available in 19 of the 23 deaths to allow an analysis to evaluate the toxicological significance of furanylfentanyl. Of these, furanylfentanyl was either the cause of death or is likely to have contributed to death (even in presence of other substances) in 17 cases. Whilst other drugs may have contributed some toxicity, a synergistic and/or additive effect with furanylfentanyl would have been likely (e.g. other central nervous system depressants such as ethanol, benzodiazepines, other opioids, etc.). Nevertheless, the pharmacological opioid nature of furanylfentanyl means the primary toxic contribution could be attributed to the drug and death may not have occurred if furanylfentanyl had not been used. In 2 cases, furanylfentanyl may have contributed to toxicity/death but other drugs were present that may be also toxicologically significant and contributed. Overall, there is no defined 'fatal' concentration that can be assigned to furanylfentanyl but in 17 cases where measured, post-mortem blood concentrations between 0.2 to 1.54 µg/L and between 0.33 to 2.74 ng/g blood were recorded (the latter somewhat but not exactly equivalent to µg/L).

Circumstances of death

In 18 of the 23 cases, it was reported that the individuals were found dead. Of these, at least 12 were found in a home environment (their own or someone else's). Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxications). In 5 cases drug paraphernalia was found at the scene of death, including used injecting equipment. Information on the circumstances of death for the remaining 5 cases was not available.

Where known, the routes of administration were by intravenous injection, snorting, and injection/oral.

Ability to operate machinery and drive

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

Chronic toxicity

No studies were identified that investigated the chronic health effects of furanylfentanyl and/or its metabolites.

Abuse liability and dependence potential

There have been no studies that have investigated the dependence and/or abuse potential of furanylfentanyl. Given what is currently known about the pharmacology of furanylfentanyl, including some similarities to other fentanils and opioid narcotic analgesics, it is reasonable to assume that the substance has both 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 furanylfentanyl 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 furanylfentanyl are not available. In addition, risk of accidental exposure needs to be considered.

Extent, frequency, and patterns of use

There are no prevalence data on the use of furanylfentanyl in the European Union or elsewhere, but the available information does not suggest wide use of the substance.

Based on its known pharmacology and that it is sold as a 'legal' replacement to illicit opioids, it would be expected that furanylfentanyl may be sought by those looking for substitutes to opioids, such as heroin and prescription opioids. It also appears that there is interest in this substance by some psychonauts.

The available data suggests that furanylfentanyl is sold online in small and wholesale amounts as a 'research chemical', typically as a powder. It has also been sold as

ready-to-use nasal sprays. Furanylfentanyl may also be sold on the illicit opioid market, as suggested by seizures where it was found in mixtures with other opioids such as heroin, U-47,700, fentanyl, 2-fluorofentanyl, 4F-isobutyrylfentanyl and carfentanil. In these cases, it is reasonable to assume that these individuals will not be aware that they are consuming furanylfentanyl.

Availability and quality on the market

A total of 143 seizures have been reported by 13 Member States and Norway. The single largest seizures of powder were 101 g made by customs and 276 g made by police; while the largest seizure in liquid form was 974.5 mL made by police. Many of the seizures appeared to be made at street-level as powders and liquids. There have also been a small number of tablets seized as well as some herbal material that appeared to be branded as a 'legal-high'-type product. While these quantities may appear relatively small they should be considered in the context of the high potency of furanylfentanyl.

A structured search by the EMCDDA in December 2016 of online vendors of furanylfentanyl on the surface web identified 46 vendors. More than half appeared to be based in China (including Hong Kong), with a small number of vendors apparently based in, among other countries, the United States and the United Kingdom. Half of the sites listed quantities and prices.

Furanylfentanyl was typically offered in powder form and listed as a 'research chemical, not fit for human consumption'. The amounts offered ranged from 1 g (EUR 54) up to 5 kg (corresponding to EUR 5.9 per 1 g).

One site offered furanylfentanyl as a ready-to-use nasal spray and also liquid intended for vaping in electronic cigarettes. This site also offered furanylfentanyl in powder form mixed with either mannitol (ratio of 1:10) or caffeine (ratio of 1:25).

Furanylfentanyl has also been sold on darknet marketplaces.

Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviours of users of furanylfentanyl. Nonetheless, information from police seizures as well as investigations into deaths indicates that furanylfentanyl is available to and being used by high-risk drug users, including opioid users. The

available information, including from user websites, suggests that some may use furanylfentanyl as a substitute for illicit opioids and prescription opioids; this includes for self-medication, such as the alleviation of pain and/or opioid withdrawal. Finally, some users (such as psychonauts) may be experimenting with this opioid.

Information from user websites suggests that users are generally aware of the opioid-like (wanted and unwanted) effects of this substance. In addition, information from police seizures suggests that some users, particularly those consuming furanylfentanyl in mixtures with other illicit opioids such as heroin, may not be aware that they are consuming the substance.

In most of the acute intoxications suspected to involve furanylfentanyl that were reported to the EMCDDA, the patients were reported to have taken 'furanylfentanyl'.

The available information, including deaths reported by the Member States and from user websites, suggests that furanylfentanyl is used in the home environment. In the majority of the deaths reported to the EMCDDA the individuals were found dead, often in a home environment (their own or someone else's). It appears that in at least some of these cases the poisoning with furanylfentanyl was so severe that they were unable to call for help.

Information from the deaths reported to the EMCDDA found that in almost half of the deaths, furanylfentanyl was the sole opioid present, suggesting that they may have had no tolerance to opioids. In addition, polydrug use was common, including the use of other CNS depressants.

Nature and extent of health consequences

While information on the nature and extent of health consequences related to furanylfentanyl are limited, there are a number of general considerations related to fentanils as a group.

Among other adverse effects, opioid analgesics, such as fentanyl, produce dose-dependent respiratory depression. This risk is greater in persons with no tolerance to opioids. Similar to other fentanils in overdose, the most serious acute risk arising from the use of furanylfentanyl appears to be from profound and rapid respiratory depression, which can lead to apnoea, respiratory arrest, and death. This risk may be exacerbated given: the difficulty of diluting fentanils; the lack of experience of users with this new substance (in terms of a lack of familiarity with how to use it, the

effects and dose of the substance); the concomitant use of other CNS depressants (such as other opioids, benzodiazepines, gabapentinoids, and ethanol); in some cases no apparent tolerance to opioids; and, the environment in which the substance is used — typically in the home environment.

In the past few years, new dosage forms — such as ready-to-use nasal sprays, home-made transdermal patches 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.

Clinical experience with poisonings has found that the antidote naloxone will reverse poisoning (overdose) caused by furanylfentanyl. However, repeated doses may be required to fully reverse poisoning. Clinical and community experience in treating poisonings caused by exposure to fentanils supports this assertion.

In the past two years a number of outbreaks of mass poisoning caused by fentanils have been reported particularly in the United States and Canada. These types of outbreaks have had the potential to overwhelm emergency departments and 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 include a review of the availability of naloxone to users through take-home naloxone programmes.

Accidental exposure of furanylfentanyl and other fentanils — such as skin contact, inhalation, or ingestion — also poses 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 custodial settings and postal services. In addition to exercising extreme caution when handling materials suspected to contain fentanils, working environments and personnel should be equipped with

appropriate protective equipment. The antidote naloxone should be readily available to personnel in sufficient quantities; training in resuscitation and naloxone administration should also be available.

Adding to these challenges is evidence from Europe, the United States, and Canada that fentanils are being sold to unsuspecting users in/as heroin, counterfeit medicines (including 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.

Long-term consequences of use

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

Conditions under which the substance is obtained and used

There is limited information on the conditions which furanylfentanyl is obtained and used. It appears furanylfentanyl has been sold on the surface web and darknet marketplaces, typically as powders but also as ready-to-use nasal sprays. A small number of e-liquids for use in electronic cigarettes have also been reported.

Furanylfentanyl has also been advertised on darknet marketplaces. In some cases the substance also appears to be sold by street-level drug dealers, including on the illicit opioid market.

A small number of cases have confirmed that furanylfentanyl has been advertised and sold on the darknet as other opioids (including methadone, carfentanil, fentanyl). Two samples containing furanylfentanyl were purchased as the synthetic opioid U-47,700.

Overall, furanylfentanyl may be directly sought by some users, whilst others, such as those that purchase it at street-level, may be unaware that they are using furanylfentanyl. This presents an inherent risk to the individuals.

Social risks

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

Individual social risks

There is no information on whether the use of furanylfentanyl causes individual social risks; however, they may have some similarities with those associated with the use of illicit 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 furanylfentanyl on the direct social environment; however, they 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 furanylfentanyl on society as a whole.

As discussed above, accidental exposure of furanylfentanyl and other fentanils — such as skin contact, inhalation, or ingestion — also poses 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 custodial settings and postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in resuscitation and adequate provision of naloxone to reverse poisoning.

Economic costs

There are no data on the effects of furanylfentanyl in respect to its health and social costs. However, it is likely

that even at low prevalence this drug has the potential to generate relatively high costs to health services.

Possible appeal to specific population groups

Whilst no specific examples are available on the possible appeal of furanylfentanyl to specific user groups, it is reasonable to assume furanylfentanyl may be sought by those looking for substitutes for illicit opioids, such as heroin and/or prescription opioids.

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

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

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

In the cases where the origin of the seizures/collected samples reported to the EMCDDA was known, the country of origin indicated was: Poland (20 seizures); the United Kingdom (1) and China (1).

Information from seizures in four Member States that were reported to Europol shows that some furanylfentanyl on the market in Europe has been produced by chemical companies based in China.

In addition to importation, the seizure of an illicit laboratory in Europe in 2013 that was producing fentanils, that may have included furanylfentanyl, suggests that the production in Europe cannot be excluded. This recent case demonstrates the capability to manufacture fentanils exists within the European Union.

In 7 seizures made by Belgian customs the country of destination of the seizure was: Spain (1), Germany (3), France (1), the Netherlands (1) and Slovenia (1).

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 WHO informed the EMCDDA that furanylfentanyl was not currently under assessment nor had it been under assessment by the United Nations system.

On 12 May 2017, WHO informed the EMCDDA that furanylfentanyl will be reviewed at the 39th Expert Committee on Drug Dependence that will take place in November 2017.

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

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

- In the Czech Republic, furanylfentanyl is included in the amendment of Government Regulation No. 463/2013 Coll., which entered into force on 1 March 2017.
- 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 Slovenia, furanylfentanyl was classified as a 'category 1 illicit drug', which includes 'psychoactive substances that are extremely dangerous to health due to serious consequences that may result from abuse and that are not used for medicinal purposes'. The amended decree on the classification of illicit drugs was published in the Official Gazette of the Republic of Slovenia on 24 March 2017.
- In Sweden, furanylfentanyl is regulated as a narcotic, as of 25 January 2017.
- 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 ⁽¹⁰⁾.
- 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 ⁽¹¹⁾.

Germany reported that it is still under consideration whether furanylfentanyl is controlled under specific NPS control legislation.

Norway reported that furanylfentanyl is controlled by the Medicinal Products Legislation.

Fourteen Member States (Belgium, Bulgaria, Croatia, France, Greece, Ireland, Italy ⁽¹²⁾, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, and Spain) reported that furanylfentanyl is not subject to control measures at the national level.

⁽¹⁰⁾ In addition, since 5 May 2017, furanylfentanyl has been controlled under the newly defined generic definition for a group of fentanyl analogues by ministerial decree No. 6/2017. (V. 2.) that amended decree No. 55/2014 (XXII.3.) on New Psychoactive Substances.

⁽¹¹⁾ There is a recommendation of the Risk Assessment Team to place furanylfentanyl on the list of controlled substances in schedules of act of counteracting drug addiction.

⁽¹²⁾ In February 2017, the National Institute of Health, following the formal request of the Ministry of Health, proposed the inclusion of furanylfentanyl in Table I of Presidential Decree 309/90 of illicit psychotropic substances.

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 furanylfentanyl 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.

Furanylfentanyl was controlled in China as of the 1 March 2017. This control measure may at least deter the open manufacture and sale of this substance by chemical companies in this country, which are linked to the supply of the substance in Europe.

There are no studies on the possible consequences of such control measures on furanylfentanyl. 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 furanylfentanyl 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 furanylfentanyl 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 furanylfentanyl 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 furanylfentanyl 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 furanylfentanyl 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.

Conclusion

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) is a synthetic opioid and is structurally related to fentanyl, a controlled substance widely used in medicine as an adjunct to general anaesthesia during surgery and for pain management. Currently available information suggests that pharmacologically furanylfentanyl is a narcotic opioid analgesic broadly similar to fentanyl.

Furanylfentanyl has been available in Europe since at least June 2015 and has been detected in 16 Member States and Norway. The detected quantities are relatively small; however, they should be considered in the context of the potency of furanylfentanyl.

Furanylfentanyl is sold online as a 'research chemical', typically as a powder and as ready-to-use nasal sprays, in small and wholesale amounts. Limited information from seizures suggests that furanylfentanyl may have also been sold on the illicit opioid market.

Typically, the substance has been administered by nasal spray, orally and by nasal insufflation. Other routes of administration, including injecting, and vaping of e-liquids have also been reported. In the literature, smoking has also been reported as a route of administration. In addition, user reports indicate that blotters are also a possible route of administration.

Concerns exist over novel ways of administering fentanils including furanylfentanyl. These include nasal sprays, e-liquids for vaping, and home-made transdermal patches. These may have the potential to make the use of fentanils easier and more socially acceptable.

Eleven acute intoxications suspected to be due to furanylfentanyl have been reported in Europe. The clinical features were generally consistent with opioid-like toxicity and included life-threatening effects.

Clinical experience suggests that naloxone works as an antidote to poisoning caused by furanylfentanyl. Treatment may require repeated doses.

Between November 2015 and February 2017, 23 deaths have been reported by 6 countries where furanylfentanyl was detected post-mortem. In the majority of cases other drugs were also detected with furanylfentanyl. In at least 10 deaths, furanylfentanyl was reported to be either the cause of death or to have contributed to death.

There have also been reports of severe non-fatal intoxications and deaths from the USA and Canada.

Due to the nature of furanylfentanyl both non-fatal intoxications and deaths are likely to be under-detected and under-reported.

Information from police seizures as well as investigations into deaths indicates that furanylfentanyl is available to and being used by high-risk drug users, including opioid users.

Accidental exposure to furanylfentanyl, as well as to other fentanils, poses a risk to law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as to those in custodial settings and postal services. Specific risks and appropriate measures to reduce these risks should be identified and implemented. This may include appropriate protective equipment, training in resuscitation, and making naloxone readily available to relevant personnel in sufficient quantities in the event of poisonings.

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 furanylfentanyl 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 furanylfentanyl on the market in Europe has been produced by chemical companies based in China. In addition to importation, the seizure of an illicit laboratory in Europe in 2013 that was producing fentanils, that may have included furanylfentanyl, suggests that the production in Europe cannot be excluded. This case demonstrates the capability to manufacture fentanils exists within the European Union.

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

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

Ten Member States and Turkey control furanylfentanyl under drug control legislation and three Member States and Norway control furanylfentanyl under other legislation.

As for any new psychoactive substance, many of the questions related to furanylfentanyl 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 furanylfentanyl 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 furanylfentanyl 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 furanylfentanyl. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, since furanylfentanyl was first detected at least eight new fentanils and a number of other new opioids that may replace furanylfentanyl have appeared / 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 furanylfentanyl to users, practitioners, policy makers, decision makers and those who may be at risk of accidental exposure. 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.

ANNEX 1

Technical report on *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl)

Report prepared by

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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 on the information exchange, risk-assessment and control of new psychoactive substances ⁽²⁾ (EMCDDA, 2017c); and,
- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, Internet drug discussion forums and related websites, and online vendors selling furanylfentanyl.

Search strategy

Literature searches used both chemical structure and text queries in online databases; searches were conducted in May 2017. 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) and Reaxys[®] (Elsevier) databases using both the exact structure of furanylfentanyl and a similarity search. Structural and text-based searches in SureChEMBL patent database retrieved three and two relevant hits, respectively.

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), *Web of Science™* (Thomson Reuters), and in popular English-language drug forums. The search term used were:

'furanylfentanyl', 'furanyl-fentanyl', 'furanyl fentanyl', 'Fu-F', 'fentanyl furanyl analogue'.

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

Cursory, though repeated, inspections of English-language Internet forums covered *Bluelight*, *Drugs-forum*, *ecstasydata.org*, *Erowid*, *Eve&Rave*, *Reddit* and *The Vespiary*.

Additionally, the scientific networks of the authors were contacted to obtain information.

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) is a furan-2-carboxamide derivative of *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine and structurally related to fentanyl, which is a propionamide (Table 1). Furanylfentanyl contains one basic nitrogen atom in the piperidine ring readily forming salts with organic or inorganic acids ⁽³⁾.

⁽¹⁾ EMCDDA contract (ref. CT.17.SAT.0031.1.0).

⁽²⁾ OJ L 127, 20.5.2005, p. 32.

⁽³⁾ Note that 'furanylfentanyl' can refer to 2- and to 3-furanylfentanyl although in this report it refers only to the 2-isomer.

Furanylfentanyl is a close structural relative of fentanyl^(4,5), which is a fast and short-acting synthetic opioid that has been widely used in clinical practice as an adjunct to general anaesthesia during surgery and for postoperative pain management. Furanylfentanyl is also structurally related to acetylfentanyl and acryloylfentanyl, which were both the subject of an EMCDDA–Europol Joint Report in December 2015 and December 2016 following more than 30 deaths and more than 45 deaths, respectively (EMCDDA, 2016a, EMCDDA, 2017a). In February 2017, a risk assessment meeting on acryloylfentanyl was convened under the auspices of the Scientific Committee of the EMCDDA following the request by the Council of the European Union (EMCDDA, 2017b).

Furanylfentanyl is known from the scientific literature only.

Pharmacologically, furanylfentanyl is an opioid receptor agonist.

Fifteen fentanils are controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol: 3-methylfentanyl, 3-methylthiofentanyl, acetyl-alpha-methylfentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, para-fluorofentanyl, thiofentanyl, acetylfentanyl and butyrfentanyl are controlled under Schedule I and IV; alfentanil, fentanyl, sufentanil and remifentanil are controlled under Schedule I. The controls on acetylfentanyl and butyrfentanyl entered into force in 2016 and 2017.

Names and other identifiers

Systematic International Union of Pure and Applied Chemistry (IUPAC) name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide.

Chemical Abstract name: *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-furancarboxamide.

Other names: *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-furamide; 2-furanylfentanyl, 2-furanylfentanyl; *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylfuran-2-carboxamide; 1-(2-phenylethyl)-4-(*N*-phenyl-2-furoylamido)piperidine, *N*-(1-(2-phenylethyl)-4-piperidinyl)-*N*-phenylfuran-2-carboxamide.

Commonly used names: furanylfentanyl, furanyl fentanyl, furanyl-fentanyl, 2-furanylfentanyl, 2-furanylfentanyl, despropionyl furanylfentanyl,

despropionyl furanylfentanyl, furanylfenta and furanylfentanyl (Finnish).

Chemical Abstract Service Registry Numbers (CAS RNs)⁽⁶⁾

101345-66-8: free amine

101365-56-4: hydrochloride salt

PubChem SID: 313063233⁽⁷⁾

IUPAC International Chemical Identifier Key (InChI Key)⁽⁸⁾: FZJVHWISUGFFQV-UHFFFAOYSA-N

SMILES⁽⁹⁾: O=C(C1=CC=CO1)N(C2=CC=CC=C2)C3CCN(CCC4=CC=CC=C4)CC3

Street names: Fu-F

Identification and analytical profile

Physical description

Melting point: hydrochloride (HCl) salt: 235°C (dec.) (Huang et al., 1985, 1986) and 232.7°C (SWGDRUG, 2016a). The hydrochloride salt has been described as a white powder (SWGDRUG, 2016a). Furanylfentanyl contains one basic nitrogen atom in the piperidine ring, which can readily form salts with organic or inorganic acids. Solubility data for furanylfentanyl base or its hydrochloride salt could not be found but an improved aqueous solubility is expected to occur with the hydrochloride salt. An impure sample of furanylfentanyl obtained from a test purchase was reported as soluble in dichloromethane and methanol and partially soluble in water. Whether the insoluble residues represented furanylfentanyl or impurities detected in the sample was not reported (Slovenian National Forensic Laboratory, 2015). The melting point for the positional furan-3-carboxamide isomer (3-furanylfentanyl, 3-Fu-F)⁽¹⁰⁾ (oxalate) was reported as 197°C (dec.) (Huang et al., 1985, 1986).

Chemical stability and typical reactions

Specific information about furanylfentanyl could not be identified.

⁽⁶⁾ 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.

⁽⁷⁾ <https://pubchem.ncbi.nlm.nih.gov/compound/13653606>

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

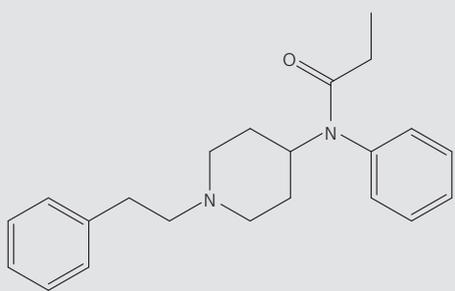
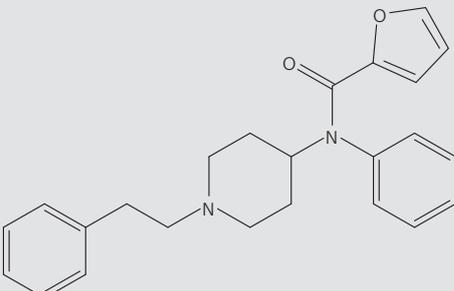
⁽⁹⁾ The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

⁽¹⁰⁾ Systematic name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-3-carboxamide. CAS RN (free amine): 101343-82-2; 101343-83-3 (oxalate).

⁽⁴⁾ <http://www.emcdda.europa.eu/publications/drug-profiles/fentanyl>

⁽⁵⁾ Fentanyl is included in Schedule I of the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol.

TABLE 1
The molecular structure, molecular formula and molecular mass of fentanyl (left) and 2-furanylfentanyl (right).

Fentanyl	Furanylfentanyl
	
C ₂₂ H ₂₈ N ₂ O 336.48 g/mol	C ₂₄ H ₂₆ N ₂ O ₂ 374.48 g/mol

Analytical profile

The ultraviolet and visible spectrum of furanylfentanyl could not be found. Various spectroscopic and mass spectrometric data have been published as summarised in Table 2. Studies on the ability to differentiate between the 2- and 3-furanylfentanyl isomers could not be identified, although the infrared spectrum of the two isomers slightly differ (SWGDRUG, 2016a, 2016b). Mass spectral may not be sufficient to allow for unambiguous differentiation so the implementation of

chromatographic and spectroscopic methods of analysis would be recommended. The aromatic region (6.0–8.0 ppm) of ¹H-NMR spectra of the two isomers are distinctly different (SWGDRUG, 2016a, 2016b).

Methods and chemical precursors used for the manufacture

No information was reported to the EMCDDA about the chemical precursors or manufacturing methods used to make the furanylfentanyl which has been detected on the drug market in Europe.

TABLE 2
Chemical analysis data published for furanylfentanyl (a)

Techniques (b)	Comment	Reference
Melting point	Characterisation of synthesised material.	Huang et al. (1985, 1986)
GC-MS, FTIR-ATR, GC-sIR, HPLC-TOF, IC, ¹ H and ¹³ C NMR	Analytical characterisation of collected impure material.	Slovenian National Forensic Laboratory (2015)
Melting point, FTIR-ATR, GC-MS, ¹ H-NMR	Analytical characterisation of DEA reference material.	SWGDRUG (2016a)
GC-MS	Analytical characterisation of reference material.	Cayman Chemical Company (2016)
LC-QTOF-MS	Analysis of human serum and urine samples.	Helander et al. (2016)
LC-QqQ-MS/MS	Analysis of post-mortem human blood samples.	Mohr et al. (2016)
GC-MS	Analysis of seized material.	Casale et al. (2017)
LC-MS/MS	Analysis furanylfentanyl and metabolites in human urine samples.	Goggin et al. (2017)
LC-QqQ-MS/MS	Analysis of furanylfentanyl in human post-mortem femoral blood samples.	Guerrieri et al. (2017)
ELISA	Method validation of a fentanyl ELISA assay in blood and urine. Furanylfentanyl showed significant cross-reactivity.	Tiscione and Wegner (2017)
LC-QTOF-MS/MS	<i>In vitro</i> and <i>in vivo</i> metabolism study.	Watanabe et al. (2017)
TD-DART-MS and IMS	Characterisation of reference material.	Sisco et al. (2017)

(a) As of 12 May 2017.

(b) GC: gas chromatography; MS: mass spectrometry; FTIR-ATR: Fourier transform infrared attenuated total reflection; sIR: solid state IR; HPLC: high performance liquid chromatography; TOF: time-of-flight; IC: ion chromatography; NMR: nuclear magnetic resonance spectroscopy; LC: liquid chromatography; QqQ: triple quadrupole; MS/MS: tandem MS; ELISA: enzyme-linked immunosorbent assay. TD-DART-MS: thermal desorption direct analysis in real time mass spectrometry; IMS: ion mobility spectrometry.

Detailed information available with regards to route-specific by-products produced during the synthesis of furanylfentanyl is not available.

Synthesis

The manufacture of furanylfentanyl relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl. Accordingly, methods developed for the multistep synthesis of fentanyl are applicable to furanylfentanyl but use a different acylating agent in the final acylation step. Correspondingly, the synthesis method of furanylfentanyl reported in the literature employed the acylation of the *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) intermediate, a precursor common to fentanyl and other fentanyl analogues, with furan-2-carbonyl chloride (Figure 1). Preparation of the 3-furanylfentanyl isomer involves the use of furan-3-carbonyl chloride as the acylating agent (Huang et al., 1985, Huang et al., 1986).

Most of these synthetic procedures are straightforward but due to the high potency of fentanils there is a serious risk of severe poisoning following accidental exposure during its manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substance. Likewise, accidental exposure of fentanils – such as skin contact, inhalation, or ingestion – pose a serious risk of poisoning to the public, law enforcement, emergency personnel, as well as medical and forensic laboratory personnel. In addition to exercising extreme caution when handling materials suspected to contain fentanils, personnel should be equipped with appropriate protective equipment. In addition, the antidote naloxone should be readily available to personnel in sufficient quantities; training in naloxone

administration and resuscitation should also be available (CDC, 2013, DEA, 2016).

The 4-ANPP precursor, as well as *N*-phenethyl-4-piperidone (NPP; a pre-precursor), were scheduled on 16 March 2017 and are listed in Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (CND, 2017). In 2010 the U.S. Drug Enforcement Administration placed 4-ANPP (named ANPP in the regulation) into Schedule II of the Controlled Substances Act in 2010 following its use as a precursor to make fentanyl in clandestine laboratories (DEA, 2010). Other routes developed for the production of fentanyl may also be used for the manufacture of furanylfentanyl. To date, there is no information on the actual method(s) used for the production of furanylfentanyl that has been detected in Europe.

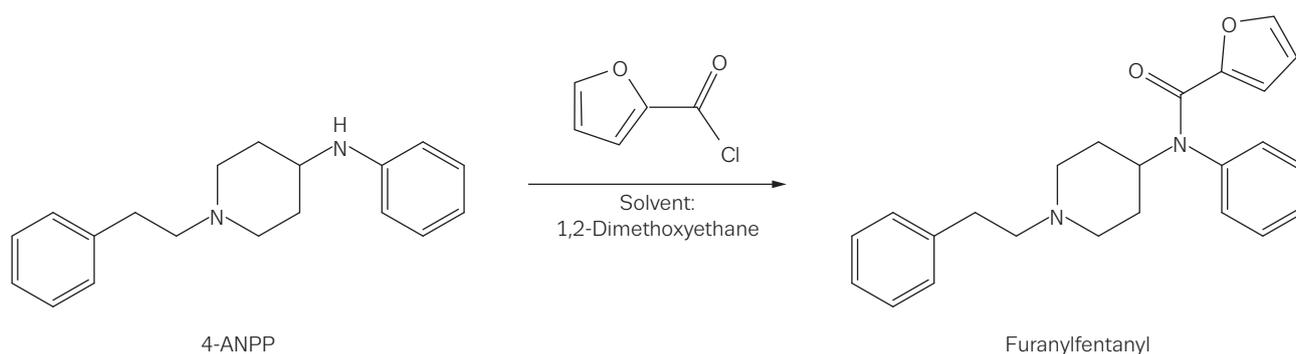
Typical impurities encountered in seized and collected samples

There are no quantitative data available on the impurities detected in seized and collected samples reported to the EMCDDA. An impure furanylfentanyl sample obtained from a test purchase from an Internet vendor apparently based in China was reported to contain organic impurities. Analysis by gas chromatography mass spectrometry suggested the presence of furan-2-carboxylic acid, which would be consistent with hydrolysed reagents used in the acylation step (furan-2-carbonyl chloride and/or furan-2-carboxylic anhydride) (Slovenian National Forensic Laboratory, 2015). In addition, two countries (Germany and Spain) reported a powdered sample each containing 'synthesis by-products' although these were not specified.

Furanylfentanyl has also been identified in samples sold on the 'deep web' as methadone, carfentanil and

FIGURE 1

Final step of the synthesis of furanylfentanyl reported by Huang et al., (1985, 1986).



fentanyl. Two samples purchased as the synthetic opioid U-47,700⁽¹¹⁾ were confirmed to contain furanylfentanyl. Other substances detected in seized powder samples, and reported by various countries include: 4-fluoroisobutyrylfentanyl (4F-iBF); *ortho*-fluorofentanyl (or 2-fluorofentanyl), cocaine and mannitol; heroin; inositol; lactose; mannitol; and paracetamol and caffeine and 4-ANPP. Two liquid samples obtained from 'darknet' vendors were reported to also contain glycerol (see section C).

In the United States, levamisole and dipyrone (metamizole)⁽¹²⁾ have been identified in furanylfentanyl samples (Logan, 2017).

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA indicate furanylfentanyl has typically been detected in powders, liquids, and occasionally in tablets and in green 'herbal' material. Some of the liquids have been detected as commercially prepared ready-to-use nasal sprays (EMCDDA, 2017c) and as e-liquids for vaping. Given the high potency associated with fentanyl analogues, the existence of blotters cannot be fully excluded⁽¹³⁾. A drug formulation intended for parenteral or intravenous analgesic administration of a range of fentanyl analogues has been suggested in a patent by Huang et al. (1985, 1986) but specific details on furanylfentanyl have not been described.

A1.3. Route of administration and dosage

Furanylfentanyl, similar to other opioids, 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). Furanylfentanyl has also been offered for sale in the form of propylene glycol/glycerol solutions (e.g. 30 mg/mL), presumably intended for vaporisation as an e-liquid in electronic cigarettes ('vaping').

Data reported to the EMCDDA regarding acute intoxications suspected to involve furanylfentanyl (section D1.2) suggests that furanylfentanyl was

administered nasally (by nasal spray), by intramuscular injection, snorted as a powder or administered orally. E-liquids containing furanylfentanyl have been reported by France in collected samples test-purchased from vendors on darknet marketplaces. 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.

These routes of administration are similar to those reported with other fentanils. Of note is the apparent recent 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, including acryloylfentanyl (EMCDDA, 2017a; EMCDDA, 2017b).

Discussions on user websites include the descriptions of blotters (YouTube, 2017⁽¹³⁾), ingestion by vaping (Reddit, 2017⁽¹⁴⁾), intravenous injection (Erowid, 2017⁽¹⁵⁾), and preparations of solutions for nasal spray application (Bluelight, 2017⁽¹⁶⁾; Drugs-Forum, 2017⁽¹⁷⁾).

Dosage

Limited information is available regarding the dose and the dose regimens of furanylfentanyl. From this it is not possible to discern the 'typical' dosages administered by users. While a range of doses have been reported, 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. Given the difficulties of collecting such data the information below should be used with caution.

Limited data reported to the EMCDDA regarding acute intoxications suspected to involve furanylfentanyl suggests that a range of doses may be used. In 2 cases 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.

Some additional information on dosage is provided in user websites. As already highlighted, the assessment of such reports is problematic not least because the purity, amount and/or composition of the substance ingested

⁽¹¹⁾ Systematic name: 3,4-Dichloro-*N*-[(1*R*,2*R*)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide.

⁽¹²⁾ Dipyrone (or metamizole (INN)), is a phenylpyrazolone analgesic-antipyretic and used as a cutting agent by Mexican drug suppliers (Logan, 2017).

⁽¹³⁾ <https://www.youtube.com/watch?v=qDPE0EYe5Ss> (last accessed 07 May 2017)

⁽¹⁴⁾ <https://www.reddit.com/user/Furanylfentanyl/> (last accessed 07 May 2017)

⁽¹⁵⁾ <https://erowid.org/experiences/exp.php?ID=109044> (last accessed 07 May 2017)

⁽¹⁶⁾ <http://www.bluelight.org/vb/threads/755118-Novel-opioid-Furanylfentanyl> (last accessed 07 May 2017)

⁽¹⁷⁾ <https://drugs-forum.com/threads/creating-a-fu-f-fent-analog-nasal-spray.281744/> (last accessed 07 May 2017)

are typically not known by the user. Moreover, the actual composition of the substance may differ over time and different geographical areas.

One website claiming to provide information on drugs and harm reduction lists the following dosage information about oral administration and 'insufflation'. Oral: 'light' 300–500 µg; 'common': 500–900 µg; 'strong' 900–1600 µg and above. Insufflation: 'light' 200–400 µg; 'common' 400–800 µg; 'strong' 800–600 µg and above (TripSit, 2017 ⁽¹⁸⁾).

Information about the dose/volumes delivered by ready-to-use or home-made nasal sprays containing furanylfentanyl could not be identified.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacodynamics

In vitro studies

The currently available data generated *via* the Drug Enforcement Administration–Veterans Affairs (DEA-VA) Interagency Agreement (DEA, 2017) suggest that furanylfentanyl binds to the μ -opioid receptor (MOR) with high selectivity ($K_i = 0.0279$ nM) over the κ - and δ -opioid receptors (KOR and DOR) with K_i values of 59.2 nM and 54 nM, respectively (Table 2) ⁽¹⁹⁾ (DEA, 2017).

Table 3 provides a summary of additional binding and functional activity data (adapted from DEA (2017)) that illustrate that furanylfentanyl ($EC_{50} = 2.52$ nM, [³⁵S]GTP γ S binding assay, $E_{max} = 55.5$ %) functioned as a MOR agonist more potent than morphine ($EC_{50} = 31.0$ nM, [³⁵S]GTP γ S binding assay, $E_{max} = 83.3$ %) and fentanyl ($EC_{50} = 17.9$ nM, $E_{max} = 81.2$ %) although it functioned less efficaciously than morphine or fentanyl, the two comparator drugs (compare E_{max} values). Furanylfentanyl also showed appreciable affinity toward KOR but showed only very low efficacy as an agonist ($E_{max} = 24.9$ %) compared to U-50,488H ⁽²⁰⁾ ($E_{max} = 81.2$ %), morphine ($E_{max} = 86.8$ %) and fentanyl ($E_{max} = 72.9$ %), respectively. Furanylfentanyl was functionally inactive

at DOR but displayed a higher affinity ($K_i = 54$ nM, [³H]DPDPE) compared to morphine ($K_i = 111$ nM, [³H]DPDPE) and fentanyl ($K_i = 242$ nM, [³H]DPDPE) (DEA, 2017).

These receptor studies have established furanylfentanyl to be potent agonist of opioid receptor types MOR and DOR. It is not known, however, whether this MOR agonist effect, which is responsible – among other physiological effects – for respiratory depression, would translate to high toxicity *in vivo*.

Animal studies

Results from animal studies could only be identified in one study. Following intravenous administration (tail vein), furanylfentanyl displayed antinociceptive effects using the mouse hot plate test ⁽²¹⁾. The ED_{50} value ⁽²²⁾ was determined as 0.02 mg/kg although data for comparator substances, such as morphine and fentanyl, were not reported. Evaluation of the 3-furanylfentanyl isomer revealed a ~4-fold drop in potency ($ED_{50} = 0.076$ mg/kg) (Huang et al., 1985, 1986). The patent gives an ED_{50} of 0.0077 mg/kg for ocfentanil (1-(2-phenylethyl)-4-[N-(2-fluorophenyl)methoxyacetamido]piperidinium oxalate), another synthetic opioid reported to EU Early Warning System and notified as a new psychoactive substance in 2013 (EMCDDA & Europol 2014).

A separate study published by Bagley et al. (1989), reporting on the analgesic properties of a range 4-(heteroanilido)piperidines, identified an ED_{50} value of 0.018 mg/kg for fentanyl in the mouse hot plate test (55°C instead of 58°C by Huang et al. (1985, 1986)), which indicates that fentanyl and furanylfentanyl have comparable analgesic potency in this animal assay. Schneider and Brune (1986) reported that fentanyl ($ED_{50} = 0.015$ mg/kg) was over 230-fold more potent than morphine ($ED_{50} = 3.5$ mg/kg) and > 1,300-fold more potent than pethidine ($ED_{50} = 20.0$ mg/kg) in the mouse hot plate test. In comparison, acryloylfentanyl ⁽²³⁾ ($ED_{50} = 0.082$ mg/kg), recently being subject to an

⁽¹⁸⁾ <http://drugs.tripsit.me/furanylfentanyl> (last accessed 07 May 2017)

⁽¹⁹⁾ K_i represents the equilibrium inhibition constant for the test drug displacing the radioligand.

⁽²⁰⁾ According to Von Voigtlander and Lewis (1982), U-50,488H refers to the methanesulfonate hydrate salt whereas U-50,488E refers to the monohydrochloride hemihydrate salt.

⁽²¹⁾ Tests the ability of antinociceptive agents to inhibit paw lick responses of mice placed in contact with a heated surface. In the study reported by Huang et al. (1985, 1986), the temperature was set at 58°C.

⁽²²⁾ The dose at which 50% of test animals meet the criteria for the analgesic response. The median effective dose (ED_{50}) can be calculated by measuring the prolongation of latency times of a response to pain after administration of the test substance at various doses as compared to untreated control.

⁽²³⁾ Systematic name: N-Phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide.

TABLE 3

Opioid receptor binding data of furanylfentanyl (modified from DEA (2017)) (e)

MOR	Furanylfentanyl	DAMGO	Morphine	Fentanyl	Naltrexone
[³ H]DAMGO binding K _i (nM)	0.0279 ± 0.0080	0.1313 ± 0.0050	0.213 ± 0.019	0.150 ± 0.030	0.0793 ± 0.0042
IC ₅₀ (nM)	0.192 ± 0.058	–	–	–	–
Hill coefficient	-0.55 ± 0.04	-0.89 ± 0.06	-0.95 ± 0.02	-0.72 ± 0.07	-0.81 ± 0.36
[³⁵ S]GTPγS binding	Furanylfentanyl	DAMGO	Morphine	Fentanyl	
Stimulation EC ₅₀ (nM)	2.52 ± 0.46	21.4 ± 4.2	31.0 ± 8.2	17.9 ± 4.3	–
Maximal stimulation (%) [*]	55.5 ± 4.3	96.8 ± 1.9	83.3 ± 5.5	81.2 ± 7.4	–
DOR	Furanylfentanyl	DPDPE-OH	Morphine	Fentanyl	Naltrexone
[³ H]DPDPE binding K _i (nM)	54 ± 15	2.96 ± 0.57	111 ± 14	242 ± 20	14.2 ± 3.1
IC ₅₀ (nM)	88 ± 26	–	–	–	–
Hill coefficient	-0.70 ± 0.07	-0.94 ± 0.10	-0.96 ± 0.02	-0.93 ± 0.09	-1.03 ± 0.12
[³⁵ S]GTPγS binding	Furanylfentanyl	DPDPE-OH	Morphine	Fentanyl	
Stimulation EC ₅₀ (nM)	>10 μM	7.22 ± 0.38	870 ± 140	1,190 ± 140	–
Maximal stimulation (%) [*]	0	100.97 ± 0.97	77.3 ± 2.3	58.0 ± 4.2	–
KOR	Furanylfentanyl	U-50,488H	Morphine	Fentanyl	Nor-BNI
[³ H]U-69,593 binding K _i (nM)	59.2 ± 6.4	0.155 ± 0.048	27.9 ± 2.7	194 ± 20	0.42 ± 0.21
IC ₅₀ (nM)	130 ± 14	–	–	–	–
Hill coefficient	-0.85 ± 0.06	-0.70 ± 0.03	-0.98 ± 0.06	-1.19 ± 0.17	-1.11 ± 0.23
[³⁵ S]GTPγS binding	Furanylfentanyl	U-50,488H	Morphine	Fentanyl	
Stimulation EC ₅₀ (nM)	60 ± 25	1.15 ± 0.22	83 ± 23	362 ± 47	–
Maximal stimulation (%) [*]	24.9 ± 1.5	93.6 ± 2.2	86.8 ± 6.0	72.9 ± 3.2	–

(e) In receptor binding experiments, transfected Chinese hamster ovary (CHO) cells expressing human δ- and κ-opioid receptors and rat μ-opioid receptors were used. Experimental details for functional activity studies are not reported. DOR: delta opioid receptor; KOR: kappa opioid receptor; MOR: mu opioid receptor; DAMGO: Tyr-Ala-Gly-Nme-Phe-Gly-ol, DPDPE: Tyr-Pen-Gly-Phe-Pen [disulfide bridge: 2-5]; U-69,593: (+)-(5α,7α,8β)-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide; U-50,488H: trans-(±)-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide methanesulfonate salt; Nor-BNI: norbinaltorphimine; U-69,593: (+)-(5α,7α,8β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide. SEM: standard error of the mean.

Numbers represent the means ± SEM from at least three independent experiments, each conducted with duplicate determinations. A Hill coefficient other than one suggests complex interactions with binding sites. Standard compounds are the agonists DPDPE (delta), U50,488H (kappa) and DAMGO (mu) and the antagonists naltrexone (delta and mu) and nor-BNI (kappa).

^{*} Maximal stimulation by test compound is normalized to the maximal stimulation by DPDPE (delta), U50,488H (kappa) or DAMGO (mu) above basal. Negative values indicate inhibition of basal [³⁵S]GTPγS binding.

EMCDDA risk assessment, exhibited 76 % of the potency of fentanyl (ED₅₀ = 0.062 mg/kg) whereas morphine (ED₅₀ = 13.9 mg/kg) only showed 4.5 % of fentanyl's antinociceptive potency in the mouse hot plate test (Zhu et al., 1981, cited in EMCDDA, 2017b).

Furanoyl analogues of 3-methylfentanyl have also been pharmacologically characterised and their activity *in vivo* and *in vitro* were compared to morphine and fentanyl using the mouse hot plate test (55°C) (Lalinde et al., 1990). The ED₅₀ values for the antinociceptive activities of the *cis*- and *trans*-isomers of 3-methyl-furanylfentanyl were 0.005 and 0.082 mg/kg, respectively; the relevant ED₅₀ values for morphine and fentanyl were 7.3 and 0.018 mg/kg, respectively. The K_i values in the [³H]naloxone binding inhibitory assay for *cis*- and *trans*-methyl-furanylfentanyl, morphine and fentanyl were 0.30, 0.40, 2.1 and 2.16 nM, respectively (Lalinde et al., 1990).

Pharmacokinetics

Available clinical data suggest that furanylfentanyl is detectable as the parent drug in a variety of biological matrices such as urine (Goggin et al., 2017, Watanabe et al., 2017), post-mortem blood (Guerrieri et al., 2017) and serum (Helander et al., 2016). A recent *in vitro* investigation using human hepatocytes revealed the detection of 14 furanylfentanyl metabolites (Watanabe et al., 2017) (Figure 2) and a comparison with human post-mortem urine samples suggested the identification of nine metabolites (D1, D2, D4–D8, D10, D14) with 4-ANPP (metabolite D14), dihydroxy-dihydrofuranylfentanyl (D10) and D7 being particularly abundant. 4-ANPP might also be detectable in biofluids when present as a synthesis by-product. In contrast to what was found after incubation with hepatocytes, the desphenethyl metabolite D6 ('norfuranylfentanyl' (24))

(24) Systematic name: N-Phenyl-N-(piperidin-4-yl)furan-2-carboxamide.

seemed to have played a comparatively minor role in its detectability in human urine samples (Watanabe et al., 2017). A metabolism study involving butyrfentanyl⁽²⁵⁾ revealed that the corresponding norbutyrfentanyl species⁽²⁶⁾ was abundantly formed under *in vitro* conditions using pooled human liver microsomes (predominantly catalyzed by CYP3A4 but also CYP1A2, 2C8, and 2C19). The analysis of a post-mortem blood sample suggested a comparatively minor abundance of this; however, the detection of clarithromycin, a known potent CYP3A4 inhibitor, was also reported, which might have impacted on the formation of the metabolite. Post-mortem redistribution and/or contributions from variations in enzyme phenotypes might also have accounted for this observation (Steuer et al., 2016).

Given that some of the detected metabolites (e.g. 4-ANPP, or D14, and its hydroxylated derivatives) are not specific for furanylfentanyl, a suggested target for specific furanylfentanyl-related intoxication would have to include a species carrying the biotransformation products associated with the furan ring, such as D10 and/or D7 (Watanabe et al., 2017). While specific information for furanylfentanyl is not available, it should be noted that furanyl moieties can potentially lead to the formation of unstable and reactive metabolites which are known to cause hepatic and renal necrosis (Peterson, 2013) In addition to the unmodified molecule, 4-ANPP,

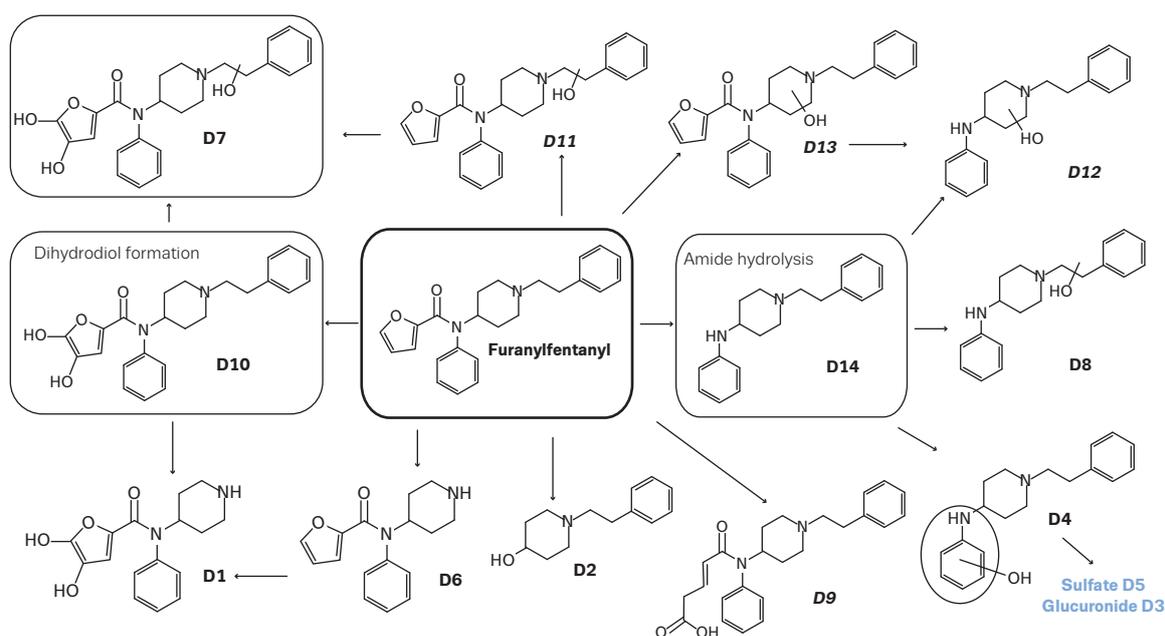
its sulfate and the dihydrodiol metabolite (and occasionally norfuranlylfentanyl) were also detected in human urine samples obtained from pain management programs of individuals who tested positive for 6-acetylmorphine (Goggin et al., 2017).

In 8 post-mortem cases in which furanylfentanyl was detected, 4-ANPP was reported in 5 aorta blood samples (Mohr et al., 2016).

There is some information on the biological activity of 4-ANPP using intact guinea pig ileum preparations. Compared to fentanyl ($IC_{50} = 4 \text{ nM}$), 4-ANPP was significantly less potent in inhibiting contractions of ileum segments induced by coaxial electrical stimulation ($IC_{50} = 12,000 \text{ nM}$). 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⁽²⁷⁾, the activity ($IC_{50} = 240 \text{ nM}$) of which was found to lie between morphine and pethidine ($IC_{50} = 1,300 \text{ nM}$), and the benzylic alcohol type derivative of fentanyl which had an IC_{50} value of 50 nM. This latter biotransformation product is related to furanylfentanyl metabolite D11 (Figure 2). Further studies are required to assess the formation of the corresponding furanylfentanyl metabolite and whether this substance would exert biological activity.

FIGURE 2

Suggested metabolic pathway of furanylfentanyl based on incubation with human hepatocytes and detection in human urine samples (Watanabe et al., 2017). Enclosed metabolites: major metabolites detected in hydrolysed human urine samples; italicized metabolites: only found either under *in vitro* or *in vivo* conditions.



⁽²⁵⁾ Systematic name: *N*-Phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl] butanamide.

⁽²⁶⁾ Systematic name: *N*-Phenyl-*N*-(piperidin-4-yl)butanamide.

⁽²⁷⁾ Systematic name: *N*-[1-[2-(4-hydroxyphenyl)ethyl]piperidin-4-yl]-*N*-phenylpropionamide.

Inter-individual genetic variability in metabolising enzymes

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 address the toxicological consequences of such polymorphisms.

Interactions with other substances and other interactions

Specific information about furanylfentanyl could not be identified although it seems conceivable that interactions observed with fentanyl (EMCDDA, 2017b, Preston, 2016) might equally apply. For example, should furanylfentanyl 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) ⁽²⁸⁾ may result in increased plasma concentration of furanylfentanyl. This could increase the risk of poisoning, including potentially fatal respiratory depression.

The concomitant use of other central nervous system (CNS) depressants, including other opioids, sedatives/hypnotics (such as the benzodiazepines and the z-drugs), ethanol, gabapentinoids (pregabalin and gabapentin), tranquillisers, sedating anti-histamines, and skeletal muscle relaxants 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 is also seen with furanylfentanyl.

⁽²⁸⁾ 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&is-NewQuery=true

Effects on ability to drive and operate machines

No studies of the effects of furanylfentanyl 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 furanylfentanyl.

A3. Psychological and behavioural effects

Information on the psychological and behavioural effects of furanylfentanyl is limited to serious adverse events reported to the EMCDDA and self-reported experiences from user websites. From the limited data available, it appears that the psychoactivity of furanylfentanyl shares some similarities with other opioid analgesics such as fentanyl and heroin, including relaxation and sedation.

One user described a steep dose-response curve with a very small gap between 'unnoticeable' effects (intravenous administration) and severe adverse effects ⁽²⁹⁾. Some user reports also suggest a rapid development of tolerance.

A4. Legitimate uses of the product

Furanylfentanyl 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 furanylfentanyl is used for other legitimate purposes.

There are no reported uses of furanylfentanyl 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 CAS Registry Number returned no results.

There is no marketing authorisation (existing, ongoing or suspended) for furanylfentanyl 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, 2017c).

⁽²⁹⁾ <https://erowid.org/experiences/exp.php?ID=109044> (last accessed 16 April 2017)

There is no information to suggest that furanylfentanyl 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 furanylfentanyl 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 furanylfentanyl in animal models.

B2. Human data

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

The limited information available from user websites suggests that some users of furanylfentanyl report an urge to re-dose, an apparent 'rapid' development of tolerance, as well as symptoms suggestive of withdrawal.

While no specific data exists for furanylfentanyl, 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 furanylfentanyl.

Section C. Prevalence of use

Information from seizures, collected and biological samples

Furanylfentanyl was formally notified on 3 November 2015 by the EMCDDA on behalf of the Finnish national focal point, in accordance with Article 4 of the Council Decision. The Reporting Form details a seizure of 0.2 g of pale brown powder that was seized on 29 June 2015 by customs in incoming mail arriving from Poland. The identification and analytical characterisation was initially based on GC-MS and LC-MS analysis, followed by NMR confirmation performed by the Swedish National Forensic Centre.

Although the first official reported detection of furanylfentanyl in Europe was from June 2015, an illicit laboratory was seized in Europe in 2013 that was producing fentanils which may have included furanylfentanyl⁽³⁰⁾, suggests that the production in Europe cannot be excluded. This case demonstrates the capability to manufacture fentanils exists within the European Union.

Since then, a total of 16 Member States and Norway have reported detections of furanylfentanyl⁽³¹⁾ (EMCDDA, 2017c).

Information from seizures

A total of 13 Member States (Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Luxembourg, Poland, Sweden and the United Kingdom) and Norway reported seizures⁽³²⁾ of furanylfentanyl to the EMCDDA and/or Europol.

Information reported to the EMCDDA and Europol indicates that 143 seizures of furanylfentanyl have been reported by: Austria (5), Belgium (7), Cyprus (1), Czech Republic (1), Denmark (3), Estonia (10), Finland (20), Germany (16), Hungary (1), Luxembourg (2), Norway (1), Poland (18), Sweden (52) and the United Kingdom (6). Most of the seizures were made during 2016 and 2017 by Police or Customs. Many of the seizures appear to have been made at street-level.

Physical forms seized included: powders (92 seizures; amounting to a total weight of 1035.9 g), liquids (30; 1558.9 mL), herbal material (12; 5.75 g) and tablets (3; 45 tablets). In 6 of the cases the physical form seized was not specified.

The detected quantities are relatively small; however, they should be considered in the context of the high potency of furanylfentanyl.

⁽³⁰⁾ Preliminary analysis by LC-MS/MS revealed the presence of furanylfentanyl and traces of 4-ANPP. NMR was not performed.

⁽³¹⁾ '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.)

⁽³²⁾ Many 'seizures' relate to individual case-level data, 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 and final reports) and from individual Reporting forms submitted on an ad hoc basis.

Powders

- 92 seizures in powder form amounting to a total weight of 1035.9 g were reported by 13 Member States and Norway.
- The largest single seizure made by police, amounting to 276 g, took place in the United Kingdom in September 2016. In this case, related to a darknet vendor supplying fentanils, 5 packages weighing from 640 mg to 219 g were seized. The vendor claimed to be selling mixtures of butyrfentanyl with mannitol, but analysis of 5 samples that were reported to the EMCDDA were found to contain furanylfentanyl, with three of those also containing other substances. The seized samples included a package of white powder that contained furanylfentanyl, ortho-fluorofentanyl, cocaine (less than 1 %) and mannitol.
- The largest single seizure made by customs amounted to 101 g and took place in Belgium in October 2016 at Bierseet Airport. The final destination was Spain.
- In powder samples, furanylfentanyl has been detected in mixtures with other opioids such as heroin, U-47,700, fentanyl, 2-fluorofentanyl, 4F-isobutyrfentanyl (4F-iBF) and carfentanil. It has also been detected with cocaine, caffeine, paracetamol, and sugars/sugar alcohols (lactose, mannitol, inositol).
- Seized powders have typically been described as white; in 1 case, a beige powder was reported (Norway).
- In a seizure of powder reported by Germany, the powder was found in a plastic bag and labelled as '2ha-IF'.
- Information on the purity of powders containing furanylfentanyl was available for 5 samples reported by Finland (4) and Belgium (1). Two of the samples from Finland were found to contain 100 % pure furanylfentanyl; one was found to contain 8 % furanylfentanyl, 48 % U-47,700, and paracetamol (not quantified); while the remaining sample contained 60 % furanylfentanyl and 4.5 % U-47,700. The sample reported by Belgium contained a mixture of furanylfentanyl and 4F-iBF (1 to 5 parts).

Liquids

- 30 seizures of furanylfentanyl in liquid form amounting to a total of 1558.9 mL were reported by 3 Member States: Austria (2), Finland (3) and Sweden (25).
- The largest seizure of furanylfentanyl in liquid form amounted to 974.5 mL and was made by Finnish police in November 2016. In this case, a total of 16 samples of liquid and 4 samples of powder containing furanylfentanyl were seized.
- 25 of the samples were in the form of 'nasal sprays', 8 were reported as a 'liquid in a bottle' and in 1 case the liquid was detected in a syringe.

- The colour of the seized liquid was only reported in 1 case where it was described as a 'yellow liquid in spraybottle' (Sweden).
- Furanylfentanyl was the only reported substance in 29 seizures, and in 11 out of the 16 samples from the large seizure reported in Finland (details above).
- Quantitative data on purity was provided for 15 samples reported by Finland. Furanylfentanyl was found in concentrations ranging from 1.1 to 3.2 mg/mL (mean: 1.9, median: 1.8). In 5 of the samples, U-47,700 was also detected with furanylfentanyl, the relative concentrations of furanylfentanyl/U-47,700 in 4 of these cases were: 1.9/0.1; 1.8/0.09; 1.1/0.06 and 1.2/18 mg/mL.

Herbal material

- 12 seizures where furanylfentanyl was detected in herbal material, were reported by Poland, amounting to 5.75 g. In 5 of the seizures, the brand name 'Talizman' was used on the packaging⁽³³⁾.

Tablets

- 3 seizures of furanylfentanyl in tablet form were reported by Swedish police, with a total amount of 45 tablets seized.

Information from collected samples

A total of 16 collected samples were reported to the EMCDDA by 4 Member States: France (7), Germany (2), Slovenia (1) and Spain (6).

- 14 of the seizures were of powders, while the remaining 2 were in liquid form.
- the total amount of powder collected was 2.03 g but in most cases the quantity collected was not reported.
- 4 of the collected samples reported by France were purchases from the darknet: 2 liquids, which were found to contain furanylfentanyl mixed with glycerol, were presented as an e-liquid for vaping in an electronic cigarette (1) and as a nasal spray (1); and 2 powders, 1 bought as U-47,700 and 1 which originated in China.
- 5 of the collected samples were sold and/or purchased as U-47,700 (2), fentanyl (1), carfentanil (1) and methadone (1), respectively.

One of the samples was collected from a user that lost consciousness after snorting a white powder. The user was discharged after treatment.

⁽³³⁾ 'Talizman motocyklisty', 'Talizman 0,5g-Ziel', 'Talizman 1,0g – Ziel', 'Talizman GT 0,5g-Ziel' and 'Talizman GT 1,0g – Ziel'.

Information from biological samples

A total of 24 detections where furanylfentanyl was analytically confirmed in biological samples were reported by 5 Member States and Norway.

These related to: 23 deaths ((Estonia (4), Finland (1), Germany (4), Sweden (12), United Kingdom (1)) and Norway (1) and 1 non-fatal intoxication (Sweden).

Availability, supply, price

Data from seizures, collected samples and acute intoxications suspected to involve furanylfentanyl suggests that the substance is sold as a powder. It is also sold as ready-to-use nasal sprays. Furanylfentanyl is sold online and is available in small and wholesale amounts.

Furanylfentanyl has been detected in mixture with: U-47,700 (in 2 powders and 5 liquids reported by Finland); fentanyl and carfentanil (in some powders reported by Estonia); 4F-iBF (1 case, Germany); heroin (1, the United Kingdom); 2-fluorofentanyl, cocaine and mannitol (1, UK); caffeine (1, Sweden); inositol (1, UK); lactose (1, UK); glycerol (2, France); sorbitol (1, France); and unspecified synthesis by-products (see Section A1.1).

Information on production

Information available on the production of furanylfentanyl in Europe is limited to one case. Although the first official reported detection of furanylfentanyl in Europe was from June 2015, an illicit laboratory was seized in Europe in 2013 that was producing fentanils which may have included furanylfentanyl⁽³⁴⁾. This suggests that the production in Europe cannot be excluded.

Information on trafficking

In 7 seizures made by Belgian customs at Bierset airport the country of destination of the seizure (all in powder form) was: Spain (1 seizure amounting to 101 g), Germany (3), France (1), the Netherlands (1) and Slovenia (1). Information on the origin of the shipments is not available.

In the cases where the origin of the seizures/collected samples reported to the EMCDDA was known, the country of origin indicated was: Poland (in at least 20 seizures of powder made in Estonia (10) and Finland (10)); the United Kingdom (1 seizure of powder, reported by Cyprus) and China (1 seizure of 11 g of powder, reported by Hungary).

Information reported to Europol on the trafficking routes is limited to seizure cases reported (EMCDDA, 2017c). In all cases where the country of origin was known, China was indicated (Estonia, Germany, Luxembourg and Sweden). Although there is limited information available, it also appears that furanylfentanyl trafficked into the United States is produced in China, along with a variety of other fentanyl analogues.

In March 2017 furanylfentanyl was controlled in China. This control measure may deter at least the open manufacture and sale of this substance by such chemical companies and which are involved in the supply of the substance in that country.

Availability from Internet vendors

A structured search by the EMCDDA of online vendors⁽³⁵⁾ of furanylfentanyl on the surface web⁽³⁶⁾ was conducted in December 2016 (EMCDDA, 2017c). 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 electronic cigarettes. This site also offered

⁽³⁵⁾ 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.

⁽³⁶⁾ 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.

⁽³⁴⁾ Preliminary analysis by LC-MS/MS revealed the presence of furanylfentanyl and traces of 4-ANPP. NMR was not performed.

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 an mean price of EUR 54;
- The mean price was (in EUR per gram): 19.3 for 10 g (n = 6 sites), 9.24 for 100 g (n = 5 sites) and 5.299 for 1 kg (n = 4 sites);
- The maximum quantity offered was 5 kg with a price of EUR 29,467 (n = 1 site).

Prices were listed in United States Dollars on all 24 sites ⁽³⁷⁾.

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

In a case reported by the United Kingdom, regarding a vendor on the darknet who was selling fentanils within the UK, the following prices were listed on the site (exact substances or mixtures are not reported, prices listed in Pounds Sterling (GBP)): '£6.66 for 250 mg; £11.20 500 mg; £18.84 for 1 g; £34.15 for 2 g; £61.61 for 3.5 g; and £90.10 for 7 g'.

Prevalence of use

No studies were identified that have investigated the prevalence of use of furanylfentanyl in the general population, but the available information does not suggest wide use of the substance. Given its pharmacology and that it is sold openly as a 'legal' replacement to illicit opioids, it would be expected that those looking for substitutes for opioids, which would include individuals who use illicit opioids, such as heroin and/or prescription opioids, may seek out furanylfentanyl and other fentanils. It also appears that there is interest in this substance by some psychonauts.

Furanylfentanyl has been detected with other opioids such as heroin, U-47,700, fentanyl, 2-fluorofentanyl, 4F-isobutyrylfentanyl (4F-iBF) and carfentanil; as well as with cocaine, caffeine, paracetamol, and sugars/sugar alcohols (lactose, mannitol, inositol). The overall significance of these seizures is unclear; however, the identification of carfentanil is of serious concern given its potency. In addition, the identification of heroin and fentanyl in the seizures may suggest that furanylfentanyl is being supplied through the illicit heroin/opioid market.

⁽³⁷⁾ 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.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

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

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of furanylfentanyl and/or its metabolites in humans. However, available non-clinical pharmacology data on furanylfentanyl (Tables 2 and 3) suggests functional similarity to fentanyl and morphine, which suggests that some toxicological similarity might exist (Moffat et al., 2016).

Data from serious adverse events associated with furanylfentanyl are discussed in section D.1.2.2. Based on the data reported, the clinical features presented in cases of intoxication involving furanylfentanyl appear to be similar to those found with fentanyl and other opioid analgesics. These included unconsciousness or reduced level of consciousness, respiratory arrest or depression and miosis.

Acute intoxications reported by the Member States

A total of 11 acute intoxications associated with furanylfentanyl were reported by three countries: Germany (4 cases), Sweden (5), and the United Kingdom (2). Of these, 1 was classed as a confirmed case ⁽³⁸⁾, 1 as a probable case, and 9 as suspected

⁽³⁸⁾ This case has been published in Helander et al. (2016) as case 14 in Table 1. In addition, case 13 in Helander et al. (2016), which relates to an intoxication involving furanylfentanyl and 4-methoxybutyrylfentanyl, is the same individual as case 14. This case is not included in the main analysis below. Briefly, on arrival of the ambulance, the patient was unconscious with no response upon pain stimulation, apneic, and cyanotic. The patient had administered a liquid intranasally (by nasal spray) and, following 'unsatisfactory nasal administration' had also injected the liquid intramuscularly. 4-Methoxybutyrylfentanyl (11.0 ng/mL serum), furanylfentanyl (4.4 ng/mL serum), ethanol metabolites, MDPHP, and pregabalin were detected in biological samples taken from the patient. An unlabeled blue nasal spray brought in by the patient was analysed and found to contain mainly furanylfentanyl and <5% 4-methoxybutyrylfentanyl. Intravenous naloxone was administered (0.4 mg); the response to naloxone was not reported. The patient was treated in hospital for 2 days.

cases⁽³⁹⁾. They occurred between November 2015 and September 2016⁽⁴⁰⁾. Most of the cases were reported by poison centres.

Demographics

Of the 11 intoxications, 9 were male and 2 were female. The mean age of the male cases was 23 (median 22) and ranged from 15 to 32 years (data available for 5 cases); the female cases 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⁽⁴¹⁾, and MDPHP⁽⁴²⁾ 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

Limited information was available on the clinical features of the intoxications. Overall, the features were generally consistent with μ -opioid agonist toxicity, but this information was only available from the probable case and some of the suspected cases⁽⁴³⁾. Clinical features included reduced level of consciousness or unconsciousness (5 cases)⁽⁴⁴⁾, respiratory arrest or depression (3)⁽⁴⁵⁾ and miosis (1). In one case

tachycardia and high body temperature were also reported. 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 8 cases.

Administration and response to naloxone

In 4 cases (the confirmed case and 3 suspected cases), naloxone was administered as an antidote. In the confirmed case 0.4mg s.c. and 0.4 mg i.v. were administered (no further details available); no information on the response is available. In the 3 suspected cases, it was reported that the patients responded to treatment with naloxone (information on the dose and route are not available).

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

Seriousness and outcome

In 6 cases (the confirmed case, the probable case, and 4 suspected cases) treatment in an emergency room/hospital was required⁽⁴⁶⁾. The information was either unknown or not reported in the remaining 5 cases.

In 3 suspected cases the seriousness of the intoxication was classified as life-threatening (1 case) or severe (2). In 1 suspected case the seriousness was classed as not life-threatening. The information was either unknown or not reported in the remaining 7 cases.

In 2 cases it was reported that the patient recovered. The information was either unknown or not reported in the 9 remaining cases.

Route of administration

In the confirmed case, furanylfentanyl was administered nasally as a liquid (by nasal spray) and by intramuscular injection. In the probable case furanylfentanyl was snorted as a powder. In 5 of the suspected cases, furanylfentanyl was either 'inhaled' (1 case), administered nasally (2) or orally (2). The information was either unknown or not reported in the 4 remaining cases.

⁽³⁹⁾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, due to the lack analytical confirmation from biological samples, information on the features of the intoxication from probable and suspected cases should be interpreted with caution. Of note in this respect is that recently some products sold as 'akrylfentanyl' in Sweden actually contained fentanyl instead (Helander et al., 2017).

⁽⁴⁰⁾In addition, Germany reported a non-fatal intoxication in which furanylfentanyl and lactose were identified in a sample of the drug that was apparently used by the patient (sample not quantified). However, insufficient information was available at the time of reporting to de-duplicate with other cases.

⁽⁴¹⁾Systematic name: 1-(1-benzofuran-5-yl)-N-ethylpropan-2-amine.

⁽⁴²⁾Systematic name: 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-yl-hexan-1-one.

⁽⁴³⁾Information on the confirmed case was limited to him being alert (Reaction Level Scale (RLS) of 1), heart rate of 100/min, and blood pressure 140/80.

⁽⁴⁴⁾Including the confirmed case.

⁽⁴⁵⁾Including a suspected case which involved cardio-respiratory arrest 10 minutes after inhalation of furanylfentanyl.

⁽⁴⁶⁾Including the confirmed and probable case.

Name of the substance/product used

In 9 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 (the probable and a suspected case), furanylfentanyl was reported to have been sourced from the internet⁽⁴⁷⁾. The information was either unknown or not reported in the 9 remaining cases.

Physical form

In the confirmed case the physical form of furanylfentanyl used by the patient was a liquid in a nasal spray. In the probable case the physical form was a powder. In a suspected case the physical form was a liquid in a nasal spray. The information was either unknown or not reported in the remaining 8 cases.

Amount or dose administered

In 3 suspected cases the amount of furanylfentanyl used was reported: 5 mg nasally (1 case); 50 mg orally (1 case); 30 mg by inhalation. The information was either unknown or not reported in the remaining 8 cases.

Acute intoxications identified from other sources

In Surrey, 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 (22 cases, 51 %) lost consciousness after smoking what they believed to have been crack cocaine. Samples of the drug used by the patients were analysed and found to contain a mixture of furanylfentanyl and cocaine. It was reported that most of the overdoses occurred within a small geographic area that has a high population of homeless persons and persons who use illicit drugs, including opioids and crack cocaine. Most of the overdoses occurred in males (36 cases, 84 %); the mean age of the patients was 42 years and ranged between 18 and 63 years. The majority of patients (40 cases, 93 %) arrived at the emergency department by ambulance. Most patients (37 cases, 86 %) received injectable naloxone before arriving at the emergency department. This included 12 patients who received it only from community members, 16 who received it only from paramedics, five who received it from both community members and paramedics, one who received

it from the fire department and paramedics, and one who received it from the fire department, community, and paramedics (for two patients, the source of naloxone was not known). Of particular note is that information from first responders, the community, and emergency department staff members highlighted that patients required high doses of naloxone, in some cases up to 3.0 mg (usual dose = 0.4 mg). Most of the patients (35 cases, 81 %) were treated and discharged within a few hours, two patients left without being seen by emergency department staff, and six patients were admitted to the hospital; among these, three were transferred to the intensive care unit, one of whom died (Klar et al., 2016a; Klar et al., 2016b).

Deaths reported by the Member States

A total of 23 analytically confirmed deaths associated with furanylfentanyl were reported by six countries: Estonia (4 deaths), Finland (1), Germany (4), Sweden (12)⁽⁴⁸⁾, United Kingdom (1), and Norway (1).

Demographics

Information on demographics was available for 19 deaths. Of these, 17 were male and 2 were female. The mean age of the male decedents was 32.9 years (median 32) and ranged between 25 and 53 years; the age of the female decedents was 33 and 48 years.

Number of deaths by year

All 23 deaths occurred between November 2015 and February 2017; two deaths occurred in 2015, 19 in 2016 and 2 in 2017.

Cause of death and toxicological significance

In 10 deaths, furanylfentanyl was reported to be the cause of death or to have contributed to death; in 2 of these deaths furanylfentanyl was the sole drug present. In 3 deaths furanylfentanyl was assumed to have contributed to death. In 3 cases the cause of death was reported as an "overdose with drugs or narcotics", with no substances explicitly mentioned. In the remaining 7 cases the cause of death had not yet been established, was not known, or was not reported.

A range of other substances were found in the deaths, including: benzodiazepines, gabapentinoids (pregabalin, gabapentin), ethanol, THC, amphetamine, MDMA, cocaine, antidepressants and antipsychotics. In 11 cases, furanylfentanyl was the sole opioid present. In the remaining 12 cases, other opioids detected were:

⁽⁴⁷⁾ The probable case and a suspected case.

⁽⁴⁸⁾ Seven of the deaths reported by Sweden are also reported in Guerrieri et al., (2017).

fentanyl (6 deaths), acetylfentanyl (2), buprenorphine (2), tilidine (2), methadone (1), 4Cl-iBF (1), and tramadol (1).

No information was available regarding symptoms experienced by the decedents prior to death.

In an attempt to evaluate the toxicological significance of furanylfentanyl in the deaths reported, an assessment of the following evidence was considered in each case: presence and concentration (and pharmacological nature) of furanylfentanyl; presence and concentration (and pharmacological nature) of other drugs present (including alcohol); circumstances of death; pathological findings at post-mortem, and cited cause of death. This allowed categorisation of the significance of furanylfentanyl in the deaths as being of low significance (i.e. alternative cause of death), medium significance (i.e. furanylfentanyl may have contributed to toxicity/death but other drugs present may have been more toxicologically significant) or high significance (i.e. furanylfentanyl was cited as the cause of death or was assessed to have been likely to contribute to toxicity/death even in the presence of other drugs). In order to highlight potential interactions or contributing toxicology, the other substances found in the cases were characterised.

In 19 of the 23 deaths there was sufficient data to allow an assessment of the toxicological significance of furanylfentanyl. Of these, furanylfentanyl was either the cause of death or is likely to have contributed to death (even in presence of other substances) in 17 deaths. Whilst other drugs may have contributed some toxicity, a synergistic effect with furanylfentanyl would have been likely (e.g. other central nervous system depressants such as ethanol, benzodiazepines, other opioids, etc). Nevertheless, the pharmacological opioid nature of furanylfentanyl means the primary toxic contribution could be attributed to the drug and death may not have occurred if furanylfentanyl had not been used. In 2 cases, furanylfentanyl may have contributed to toxicity/death but other drugs were present that may be also toxicologically significant and contributed. In one case, an additional fentanyl derivative, 4-chloro-isobutyrfentanyl (4Cl-iBF) was detected (2.2 ng/g) along with a significant concentration of pregabalin (36 µg/g). In the other case, pregabalin and gabapentin were present at significant concentrations (27 µg/g and 90 µg/g, respectively) as well as fentanyl (0.38 ng/g), norbuprenorphine (1.3 µg/g), benzodiazepines (alprazolam and diazepam), alimemazine and methylphenidate. Overall, there is no defined "fatal" concentration that can be assigned to furanylfentanyl but in 17 cases where measured, post-mortem blood concentrations between 0.2 to 1.54 µg/L and between 0.33 to 2.74 ng/g blood were recorded (the latter somewhat but not exactly equivalent to µg/L).

Circumstances of death

In 18 deaths, it was reported that the decedents were found dead. Of these, at least 12 were found in a home environment (their own or someone else's) ⁽⁴⁹⁾, 2 were found in a bathroom (no further information provided), and 1 was found outside. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxications). In 5 cases drug paraphernalia was found at the scene of death, including used injecting equipment. Information on the circumstances of death for the remaining 5 cases was not available.

In 4 deaths, the route of administration was reported: intravenous injection (2 cases), injected/oral (1), and snorted (1).

Circumstantial information, as well as analysis of hair samples, suggests that some of decedents were high-risk drug users, including opioid users.

Deaths identified from other sources

At least 128 deaths associated with furanylfentanyl have been reported since 2015 in the United States (DEA, 2016; Mohr et al., 2016).

D2. Chronic health effects

D2.1. Animal data

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

D2.2. Human data

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

D3. Factors affecting public health risks

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

Furanylfentanyl is being sold by vendors on the Internet as a drug in its own right. It is sold in both retail and wholesale quantities. It has been sold as a 'research

⁽⁴⁹⁾ Including the bathroom (2 cases) and the couch (2 cases).

chemical' in several physical forms, including as powders and ready-to-use nasal sprays.

Limited information from seizures also suggests that furanylfentanyl is being sold on the illicit drug market, including the heroin/illicit opioid market.

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

Given the relatively recent availability of furanylfentanyl, the availability of information, degree of knowledge and perceptions amongst users concerning the substance and its effects are limited.

Information from user websites suggests that users are generally aware of the opioid-like (wanted and unwanted) effects of this substance. In addition, information from seizures suggests that some users, particularly those consuming furanylfentanyl in mixtures with other illicit opioids such as heroin, may not be aware that they are consuming the substance.

D3.3. Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviours of users of furanylfentanyl. The available information, including deaths reported by the Member States and from user websites, suggests that furanylfentanyl is typically used in the home environment.

Some users may seek out furanylfentanyl because it was sold openly as a 'legal replacement' to illicit opioids; others may be experimenting with this opioid (so called psychonauts) to explore possible novel effects; whilst others still may seek to self-medicate pain or opioid-withdrawal symptoms. It is likely that some users, particularly those consuming furanylfentanyl in mixtures with other illicit opioids such as heroin, may not be aware that they are consuming the substance.

Information from the deaths reported to the EMCDDA highlights that in 11 cases, furanylfentanyl was the sole opioid present. This suggests that approximately half of the decedents may have had no tolerance to opioids. In addition, the data also shows that polydrug use was common, including the use of other CNS depressants (Section D1.2).

D3.4. Nature and extent of health consequences

The limited information available on the pharmacology, dependence and abuse potential, and acute health effects of furanylfentanyl have been discussed above (Section A2, Section B, Section D1 and Section D2).

While the pharmacology and toxicology of furanylfentanyl largely remains unstudied, the available data, including its structural similarity to fentanyl, suggests that it is a potent opioid narcotic analgesic.

Among other adverse effects, opioid analgesics, such as fentanyl, produce dose-dependent respiratory depression. This risk is greater in opioid-naïve persons. Similar to other fentanils in overdose, the most serious acute risk arising from the use of furanylfentanyl appears to be from profound and rapid respiratory depression, which can lead to apnoea, respiratory arrest, and death. This risk may be exacerbated given:

- the difficulty of diluting fentanils ⁽⁵⁰⁾;
- the lack of experience of users with this new substance (in terms of a lack of familiarity with the effects and dose of the substance);
- the concomitant use of other CNS depressants (such as other opioids, benzodiazepines, gabapentanoids, and ethanol (alcohol));
- in some cases no apparent tolerance to opioids; and,
- the environment in which the substance is used — typically in the home environment.

In almost 80 % of the deaths reported to the EMCDDA the individuals were found dead, often in a home environment (their own or someone else's). It is reasonable to assume that in at least some of these cases the poisoning with furanylfentanyl was so severe that they were unable to call for help.

Importantly, given what is known about the pharmacology of furanylfentanyl it is reasonable to assume that the antidote naloxone will reverse poisoning (overdose) caused by exposure to the substance. Recent clinical and community experience in treating probable and suspected furanylfentanyl poisoning cases supports this assertion (Klar et al., 2016a; Klar et al., 2016b). However, due to the potency of the fentanils, their half-lives, and the dose used, larger than normal doses as well as repeated doses of naloxone may be required to fully reverse poisoning (CDC, 2013; FDA, 2016). Again, clinical ⁽⁵¹⁾and community experience in treating poisonings by fentanils, including furanylfentanyl,

⁽⁵⁰⁾ This is also reflected in data from seizures of tablets containing fentanils which have shown large variability in the amount of the substance present (de Boer et al., 2003).

⁽⁵¹⁾ Including paramedics and hospital emergency room staff.

supports this assertion (Klar et al., 2016a; Klar et al., 2016b; Sutter et al., 2017). Stocks and availability of the antidote naloxone, as well as adequacy of training in how to resuscitate poisoned patients may need to be assessed.

In a recent outbreak of poisonings in California, United States, which was caused by counterfeit analgesic medicines containing large doses of fentanyl (Sutter et al., 2017), it was highlighted that:

- Sufficient antidote stocking was an important factor as the supplies of naloxone at the hospital were quickly depleted because of the large number of patients that presented over a short period of time, as well as the need of some patients for several milligrams of naloxone as bolus dosing and prolonged infusion times.
- The hospital required emergency deliveries of naloxone to keep supplies sufficient for patient care.
- A notable clinical difference observed was not only that some patients required prolonged naloxone infusions but also the recurrence of respiratory depression in the hospital after 8 hours of observation without naloxone.

In addition to users, accidental exposure of furanylfentanyl and other fentanils — such as skin contact, inhalation, or ingestion — pose a serious risk of poisoning to the public, law enforcement, emergency personnel, as well as medical and forensic laboratory personnel (Section A).

Adding to the challenges posed by the fentanils is evidence from Europe, the United States, and Canada that they are being sold to unsuspecting users in/as heroin or other illicit opioids, counterfeit medicines (including 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 (Klar et al., 2016a; Klar et al., 2016b; HCCCSF, 2016a; HCCCSF, 2016b; SFDPH, 2015; Tomassoni et al., 2017). Non-opioid users are unlikely neither to be aware of these risks nor to have access to community-based naloxone programmes, including take-home naloxone (EMCDDA, 2015; EMCDDA, 2016b).

D3.5. Long-term consequences of use

There is no data regarding the long-term consequences of using furanylfentanyl.

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 which furanylfentanyl is obtained and used. It appears furanylfentanyl has been sold on the surface web and darknet marketplaces, typically as powders. It has also been sold as ready-to-use nasal sprays. A small number of e-liquids for use in electronic cigarettes have also been reported.

Limited information suggests that it may also have been sold on the illicit drug market, including the illicit opioid/heroin market in some countries.

In almost 80 % of the deaths reported to the EMCDDA the individuals were found dead, often in a home environment (their own or someone else's).

Data reported to the EMCDDA suggests that ready-to-use nasal sprays and e-liquids containing fentanils are increasing in availability. It will be important to study what effect, if any, these products have had on increasing physical availability, attractiveness, and social acceptance to existing and new groups of users.

Section E. Social risks

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

E1. Individual social risks

There is no information on whether the use of furanylfentanyl causes individual social risks; however, they may have some similarities with those associated with illicit opioids, including fentanyl and heroin. These may 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 furanylfentanyl on the direct social environment; however, they 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 furanylfentanyl on society as a whole.

As discussed above, accidental exposure of furanylfentanyl and other fentanils — such as skin contact, inhalation, or ingestion — also poses a serious 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 custodial settings and postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in resuscitation and adequate provision of naloxone to reverse poisoning.

E4. Economic costs

There are no data on the effects of furanylfentanyl in respect to its health and social costs. However, it is likely that even at low prevalence this drug has the potential to generate relatively high costs to health services.

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

There is no specific data on the possible effects of furanylfentanyl related to the cultural context.

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

Whilst no specific examples are available on the possible appeal of furanylfentanyl to specific user groups, it is reasonable to assume furanylfentanyl may be sought by those looking for substitutes for illicit opioids, such as heroin and/or prescription opioids.

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

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 furanylfentanyl.

In the cases where the origin of the seizures/collected samples reported to the EMCDDA was known, the country of origin indicated was: Poland (20 seizures); the United Kingdom (1) and China (1).

Information from seizures in four Member States that were reported to Europol shows that some furanylfentanyl on the market in Europe has been produced by chemical companies based in China.

In addition to importation, the seizure of an illicit laboratory in Europe in 2013 that was producing fentanils, that may have included furanylfentanyl, suggests that the production in Europe cannot be excluded. This case demonstrates the capability to manufacture fentanils exists within the European Union.

In 7 seizures made by Belgian customs the country of destination of the seizure was: Spain (1), Germany (3), France (1), the Netherlands (1) and Slovenia (1).

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

There is no information on the impact of furanylfentanyl on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances.

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

No information has been received by Europol of evidence of the same groups of people being involved in different types of crime in connection with furanylfentanyl.

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

No specific information has been received by Europol on incidents of violence in connection with furanylfentanyl.

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

No specific information has been received by Europol on incidents of money laundering or impact of organised crime on other socioeconomic factors in society in connection with furanylfentanyl.

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

There are no published data to be able to determine the impact of furanylfentanyl in this area.

F7. Use of violence between or within criminal groups

There are no published data to be able to determine the impact of furanylfentanyl in this area.

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

There are no published data to be able to determine the impact of furanylfentanyl in this area.

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Council Decision

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**COUNCIL IMPLEMENTING DECISION (EU) 2017/2170 of 15 November 2017 on
subjecting *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide
(furanylfentanyl) to control measures**

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances ⁽¹⁾, and in particular Article 8(3) thereof,

Having regard to the proposal from the European Commission,

Having regard to the opinion of the European Parliament ⁽²⁾,

Whereas:

(1) A risk-assessment report on the new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) was drawn up in accordance with Decision 2005/387/JHA by a special session of the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and was subsequently submitted to the Commission and to the Council on 24 May 2017.

(2) Furanylfentanyl is a synthetic opioid and is structurally similar to fentanyl, a controlled substance widely used in medicine for general anaesthesia during surgery and for pain management. Furanylfentanyl is also structurally related to acetylfentanyl and acrylolylfentanyl, which were both the subject of an EMCDDA–Europol Joint Report in December 2015 and November 2016.

(3) Furanylfentanyl has been available in the Union since at least June 2015 and has been detected in 16 Member States. In most cases, it was seized in powder form, but also in liquid form and as tablets. The detected quantities are relatively small. However, such quantities should be seen in the context of the potency of the substance.

(4) Twenty-two deaths associated with furanylfentanyl have been reported by five Member States. As regards at least ten of those deaths, furanylfentanyl was the cause of death or is likely to have contributed to the death. In addition, 11 acute non-fatal intoxications associated with furanylfentanyl were reported by three Member States.

(5) There is no information suggesting the involvement of organised crime in the manufacture, distribution (trafficking) and supply of furanylfentanyl within the Union. The available data suggest that furanylfentanyl is produced by chemical companies based in China.

(6) Furanylfentanyl is sold online in small and wholesale amounts as a 'research chemical', typically as a powder and as ready-to-use nasal sprays. Information from seizures suggests that furanylfentanyl may have also been sold on the illicit opioid market.

(7) Furanylfentanyl has no recognised human or veterinary medical use in the Union. There are no indications that furanylfentanyl may be used for any other purpose apart from as an analytical reference standard and in scientific research.

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

⁽²⁾ Opinion of 24 October 2017 (not yet published in the Official Journal)

(8) The risk-assessment report reveals that many of the questions related to furanylfentanyl are due to the lack of data on the risks to individual health, risks to public health, and social risks, and could be answered through further research. However, the available evidence and information on the health and social risks that the substance poses, given also its similarities with fentanyl, provide sufficient grounds for subjecting furanylfentanyl to control measures across the Union.

(9) Furanylfentanyl is not listed for control under the 1961 United Nations Single Convention on Narcotic Drugs or under the 1971 United Nations Convention on Psychotropic Substances. The substance is not currently under assessment by the United Nations system.

(10) Given that ten Member States control furanylfentanyl under national drug control legislation and three Member States control furanylfentanyl under other legislation, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would help protect the Union from the risks that its availability and use can pose.

(11) Decision 2005/387/JHA confers upon the Council implementing powers with a view to giving a quick and expertise-based response at Union level to the emergence of new psychoactive substances detected and reported by the Member States, by subjecting those substances to control measures across the Union. As the conditions and procedure for triggering the exercise of such implementing powers have been met, an implementing decision should be adopted in order to subject furanylfentanyl to control measures across the Union.

(12) Denmark is bound by Decision 2005/387/JHA and is therefore taking part in the adoption and application of this Decision, which implements Decision 2005/387/JHA.

(13) Ireland is bound by Decision 2005/387/JHA and is therefore taking part in the adoption and application of this Decision, which implements Decision 2005/387/JHA.

(14) The United Kingdom is not bound by Decision 2005/387/JHA and is therefore not taking part in the adoption of this Decision, which implements Decision 2005/387/JHA, and is not bound by it or subject to its application,

HAS ADOPTED THIS DECISION:

Article 1

The new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) shall be subject to control measures across the Union.

Article 2

By 19 November 2018 Member States shall take the necessary measures, in accordance with their national law, to subject the new psychoactive substance referred to in Article 1 to control measures and criminal penalties, as provided for under their legislation, in compliance with their obligations under the 1971 United Nations Convention on Psychotropic Substances.

Article 3

This Decision shall enter into force on the day following that of its publication in the *Official Journal of the European Union*.

This Decision shall apply in accordance with the Treaties.

Done at Brussels, 15 November 2017.

For the Council
The President
J. AAB

Participants of the risk assessment meeting, 23 May 2017

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The risk assessment report and technical annex of the publication are published in the original version that has not been edited.

About the EMCDDA

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

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

Related publications and websites

EMCDDA

| Risk assessment of new psychoactive substances — operating guidelines, 2010

EMCDDA and Europol

| EMCDDA-Europol Joint Report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]-furan-2-carboxamide (furanylfentanyl), 2017

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

| EMCDDA–Europol Early-warning system on new psychoactive substances — operating guidelines, 2007

These and all other EMCDDA publications are available from www.emcdda.europa.eu/publications

| EMCDDA Action on new drugs website: www.emcdda.europa.eu/drug-situation/new-drugs

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