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THF-F

EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] tetrahydrofuran-2-carboxamide (tetrahydrofuranylfentanyl; THF-F)

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

About this series

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

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

EUROPOL

EMCDDA–Europol
joint publication

Contents

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- the Europol National Units (ENUs) and Europol Project Synergy;
- the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway and Iceland;
- the European Medicines Agency (EMA) and the European Commission;
- the World Health Organization;
- the United States Drug Enforcement Administration.

Project team: Anabela Almeida, Rachel Christie, Helgi Valur Danielsson, Michael Evans-Brown, Ana Gallegos, Rita Jorge, Roumen Sedefov (EMCDDA) and Werner Verbruggen (Europol).

1. Introduction

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

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

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

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

2. Information collection process

In compliance with the provisions of the Council Decision, on 25 April 2017 the EMCDDA and Europol launched a procedure for the collection of information on tetrahydrofuranylfentanyl, in order to prepare the Joint Report. The information was collected mainly through the Reitox national focal points in the Member States, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway, Iceland and Liechtenstein. The EMA also provided information as relevant to the centralised procedure for authorising medicinal products. The information collection process was largely concluded by 6 June 2017.

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

Information collected by Europol

Europol asked the Europol National Units to provide information on:

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

Europol received responses from 16 Member States [2].

Information collected by the EMA

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

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

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

[2] In alphabetical order: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, Germany, Greece, Latvia, Lithuania, Luxembourg, Romania, Slovakia, Slovenia and Spain.
[3] Austria, Belgium, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Latvia, the Netherlands, Norway, Poland, Spain, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia, Czech Republic and Italy provided a response in relation to human medicinal products. France, Portugal, Slovakia and Slovenia provided a response in relation to veterinary medicinal products.

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

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

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

Information collected by the EMCDDA

The EMCDDA collected information through:

- a structured questionnaire to the Reitox national focal points. The EMCDDA received replies from 27 Member States ([5]), as well as Turkey and Norway;
- reports previously provided to the European Union Early Warning System, including EMCDDA–Europol Reporting Forms and Progress Reports and Final Reports;
- routine monitoring of open source information;
- a specific information request to the World Health Organization on whether or not tetrahydrofuranylfentanyl is under assessment by the United Nations system; and,
- a search of open source information conducted specifically for the production of the Joint Report which included: scientific and medical literature, official reports, grey literature, internet drug discussion forums and related websites (hereafter, 'user websites') and, online vendors selling tetrahydrofuranylfentanyl.

The EMCDDA would like to thank the United States Drug Enforcement Administration for kindly providing unpublished *in vitro* data on the pharmacology of tetrahydrofuranylfentanyl (US DEA, 2017).

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

3. Information required by Article 5.2 of the Council Decision

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

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

Chemical description and names

Tetrahydrofuranylfentanyl (THF-F) belongs to the 4-anilidopiperidine class of synthetic opioids. This class also includes fentanyl ([6]), which is internationally controlled and a number of other fentanils.

A total of 15 fentanils are controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol ([7]).

Tetrahydrofuranylfentanyl differs from fentanyl due to the presence of a tetrahydrofuran ring in place of an ethyl group attached to the carbonyl. Tetrahydrofuranylfentanyl is closely related to furanylfentanyl ([8]), which has been subjected to risk assessment by the EMCDDA (EMCDDA, 2017). It differs from furanylfentanyl by bearing a fully saturated furanyl ring (tetrahydrofuran), instead of an unsaturated ring (furan).

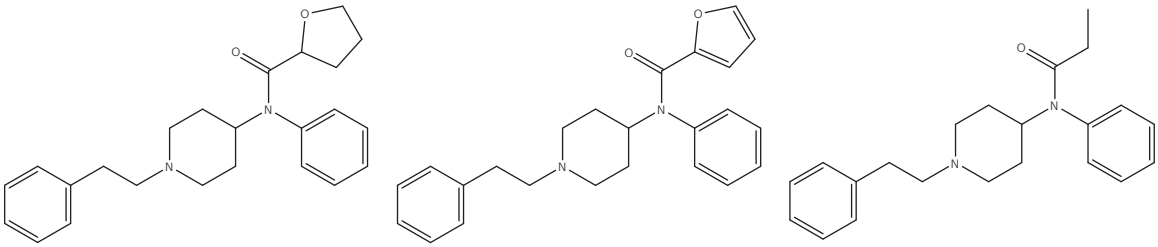
The molecular structure, molecular formula, and molecular mass of tetrahydrofuranylfentanyl are provided in in Figure 1.

([4]) Austria, Belgium, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Latvia, the Netherlands, Norway, Poland, Spain, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia, Czech Republic and Italy provided a response in relation to human medicinal products. France, Portugal, Slovakia and Slovenia provided a response in relation to veterinary medicinal products.
([5]) A reply was not received from Slovakia.

([6]) *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide.
([7]) 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.
([8]) *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]-furan-2-carboxamide

FIGURE 1

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



	tetrahydrofuranylfentanyl	furanylfentanyl	fentanyl
Molecular formula	$C_{24}H_{30}N_2O_2$	$C_{24}H_{26}N_2O_2$	$C_{22}H_{28}N_2O$
Molecular mass	378.51	374.48	336.48

Tetrahydrofuranylfentanyl has one positional isomer, which is 3-tetrahydrofuranylfentanyl. In 3-tetrahydrofuranylfentanyl, the carboxamide is attached to the 3-position of the furan ring ([9]).

Tetrahydrofuranylfentanyl contains a stereogenic centre thus allowing for the existence of a pair of enantiomers ([10]), (*S*)-tetrahydrofuranylfentanyl and (*R*)-tetrahydrofuranylfentanyl. There is no information on the actual enantiomer found in the European drug market.

The synthesis of tetrahydrofuranylfentanyl has not been described in the literature.

Commonly used names:
tetrahydrofuranylfentanyl or THF-F

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

Other chemical names:
N-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide;
N-(1-phenethylpiperidin-4-yl)-*N*-phenyltetrahydrofuran-2-carboxamide;
N-fenyl-*N*-[1-(2-fenyletyl)piperidin-4-yl]tetrahydrofuran-2-karboxamid (Swedish)

Other names and code names:
tetrahydrofuranfentanyl; tetrahydrofuran fentanyl; tetrahydrofuranyl fentanyl; tetrahydrofuran-fentanyl; THF-F; THF-fentanyl; tetrahydrofuran-F; Tetra

Chemical Abstracts Service (CAS) registry numbers ([11]):
not registered

IUPAC International Chemical Identifier Key (InCHI Key) ([12]):
OHJNHKUFSKAANI-UHFFFAOYSA-N

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

Physical description

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

There is no solubility data on tetrahydrofuranylfentanyl or its hydrochloride salt; due to its similarity to fentanyl, the free base could be expected to be sparingly soluble in water; the hydrochloride and citrate salt could be expected to have greater aqueous solubility.

Tetrahydrofuranylfentanyl is expected to be lipophilic.

([9]) Note that although 'tetrafuranylfentanyl' can refer to 2- and to 3-tetrafuranylfentanyl, in this report it will reference the 2-isomer.
([10]) Enantiomers are pairs of molecules that are mirror images of each other and therefore not superimposable. Although they have the same two dimensional molecular structure, enantiomers can exhibit marked differences in biological activity including pharmacological effects.

([11]) The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.
([12]) InChI Key is a unique, non-proprietary stuctural identifier of chemical substances useful in electronic sources.

Tetrahydrofuranylfentanyl has been seized as a liquid and in powder form. A more detailed description of seizures and collected samples can be found in section 3.2.1 and section 3.2.2.

Detection and analysis

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

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

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

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

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

3.2.1 Information provided to Europol

Europol received replies from 16 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, Germany, Greece, Latvia, Lithuania, Luxembourg, Romania, Slovakia, Slovenia and Spain).

Fifteen countries reported that they have no available information on tetrahydrofuranylfentanyl (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, Germany, Greece, Latvia, Lithuania, Luxembourg, Romania, Slovakia and Spain).

Slovenia provided information on a collected sample (section 3.2.2).

The level of production

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

The level of distribution

No information was received in relation to the distribution (seizures) of tetrahydrofuranylfentanyl.

The level of trafficking

No information was received in relation to the trafficking of tetrahydrofuranylfentanyl.

3.2.2 Information provided to the EMCDDA

The EMCDDA received responses from the 27 Member States ([5]), as well as from Turkey and Norway. Of these, two Member States (Slovenia and Sweden) reported detections of tetrahydrofuranylfentanyl ([13]).

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

Seizures

In total, 43 seizures of tetrahydrofuranylfentanyl were reported to the EMCDDA, all by Sweden. Where reported, the seizures were made by the police. Of these, 26 seizures took place in 2016, while the remaining 17 took place in 2017.

Seizures of tetrahydrofuranylfentanyl included:

- 41 seizures of liquids, amounting to a total of 698.5 mL;
- 2 seizures of powders, amounting to a total of 1.57 g.

([13]) '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.).

In all the cases, tetrahydrofuranylfentanyl was the sole substance detected. No quantitative information on purity was reported.

Collected samples
One collected sample was reported by Slovenia, which consisted of 5 g of powder test-purchased from the internet from a site based in China. In the sample, 4-aminophenyl-1-phenethylpiperidine (4-ANPP) was also detected.

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

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

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

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

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

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

3.4.1 Health risks

Pharmacology and toxicology
Limited data suggests that tetrahydrofuranylfentanyl is a μ-opioid receptor agonist that shares some similarities with opioid analgesics such as morphine and fentanyl (US DEA, 2017 ([14])).

([14]) Enantiomeric composition not specified.

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

Similar to other opioid analgesics, the most serious acute health risk from using tetrahydrofuranylfentanyl is probably respiratory depression, which in overdose could lead to apnoea, respiratory arrest and death (EMCDDA, 2017; Pattinson, 2008; White and Irvine, 1999). This risk may be greater due to: the difficulty in diluting the substance; a lack of experience with its effects and dosing; the use of other central nervous system depressants at the same time (such as other opioids, benzodiazepines, gabapentanoids and alcohol); a lack of tolerance to opioids; and, using the substance alone (such as at home) which would make it more difficult for users to call for help in the case of poisoning.

The antidote naloxone should reverse acute poisoning caused by tetrahydrofuranylfentanyl (Kim and Nelson, 2015; Ujváry *et al.*, 2017). Recent clinical and community experience in treating poisonings caused by fentanils suggests that larger than normal doses and repeated doses of naloxone may be required to fully reverse poisoning in some cases (EMCDDA, 2017).

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

3.4.2 Serious adverse events

Acute intoxications reported to the EMCDDA
In total, one acute intoxication with confirmed exposure to tetrahydrofuranylfentanyl was reported by Sweden ([15]). The case occurred in 2016.

In this case, the patient had administered *eight* actuations of a 'fentanyl' nasal spray. The poisoning was classed as severe. The clinical features were consistent with the use of an opioid *and* included decreased consciousness, respiratory depression and miosis. Naloxone was administered but the response was not reported. The only other substance detected was flunitrazolam. The patient survived.

([15]) In addition, Sweden also reported 2 acute intoxications with suspected exposure to tetrahydrofuranylfentanyl. These cases are not discussed further in this report.

Deaths reported to the EMCDDA
In total, 14 deaths with confirmed exposure to tetrahydrofuranylfentanyl were reported by Sweden. The cases occurred between 2016 and 2017.

Of the deaths, eight were male (57 %) and six were female (43 %). The males were aged between 25 and 41 years (mean 31.4, median 29); the females were aged between 29 and 38 years (mean 31.5, median 30).

A range of other substances were detected in the deaths, including other central nervous system depressants. Other opioids were only detected in three cases. Where known, most of the individuals were found dead; in at least some cases this was in a home environment. In at least 12 cases, tetrahydrofuranylfentanyl was the cause of death or contributed to the death.

3.4.3 Characteristics of users

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

3.4.4 Social risks

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

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

Similar to other fentanils, accidental exposure to tetrahydrofuranylfentanyl may also pose a risk of severe poisoning. Those at risk may include the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those working in the postal services. Where required, these risks should be assessed and appropriate procedures, training and protective measures should be implemented. This may include training in resuscitation and adequate provision of the antidote naloxone.

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

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

On 1 May 2017, the World Health Organization informed the EMCDDA that tetrahydrofuranylfentanyl is currently not under assessment and has not been under assessment by the UN system.

Since then, the World Health Organization has published a list of substances that will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017. Tetrahydrofuranylfentanyl was included in the list of substances that will be reviewed. At the time of writing this report neither a critical review nor a written recommendation had been published.

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

The first official EMCDDA–Europol notification of tetrahydrofuranylfentanyl dates from 23 December 2016 from the Swedish national focal point. The Reporting Form details the seizure of tetrahydrofuranylfentanyl in 22 ml of pale yellow liquid, seized by Swedish Police in Karlstad on 29 September 2016. The substance was analytically confirmed by GC-MS, liquid chromatography–high resolution mass spectrometry (LC–HRMS) and NMR by the Swedish National Forensic Centre. The formal notification informed on five analytically confirmed deaths associated with tetrahydrofuranylfentanyl that had occurred in Sweden between September and October 2016.

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

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

Three Member States (Latvia, Sweden and the United Kingdom) reported that tetrahydrofuranylfentanyl is controlled under drug control legislation.

Two Member States (Austria and Poland) reported that tetrahydrofuranylfentanyl is controlled under specific new psychoactive substances control legislation.

Norway reported that tetrahydrofuranylfentanyl is controlled under medicines legislation.

Twenty two Member States (Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovenia and Spain) and Turkey reported that tetrahydrofuranylfentanyl is not subject to control measures at the national level.

Slovakia did not provide information on the control status of tetrahydrofuranylfentanyl.

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

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

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

In a collected sample reported by Slovenia, the precursor 4-ANPP was also detected (section 3.2.2).

The synthesis of tetrahydrofuranylfentanyl has not been described in the literature. The manufacture of tetrahydrofuranylfentanyl relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl (Casy and Huckstep, 1988; Gupta *et al.*, 2013; Zee and Wang, 1980). Therefore the methods developed for the synthesis of fentanyl are applicable to the synthesis of tetrahydrofuranylfentanyl. Use of a different acylating agent in the final acylation step, such as tetrahydrofuranoyl chloride would produce tetrahydrofuranylfentanyl. A one-step method uses *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) and tetrahydrofuranoyl chloride for the manufacture of the substance.

Two potential precursors of fentanyl and other fentanils 4-ANPP as well as *N*-phenethyl-4-piperidone (NPP, a pre-precursor), have been recently scheduled under the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988 ([16]).

Most of the synthetic procedures are straightforward, use common laboratory equipment and precursors and detailed recipes are available on the internet ([17]). While only basic knowledge of synthetic chemistry is required, due to the potency of fentanils extreme caution is required when carrying out the final synthetic step as well as when purifying and handling the substance ([18]). Exposure of the skin and mucous membranes to fentanils as well as their inhalation pose a serious risk of accidental poisoning. In addition to exercising extreme caution, suitable personal protective equipment as well as sufficient stocks of naloxone as an antidote to poisoning following accidental exposure should be available when handling materials suspected to contain these substances (CDCP, 2013; US DEA, 2016b).

In summary, whilst the synthesis of tetrahydrofuranylfentanyl has not been described in the literature, other routes developed for the production of fentanyl may also be used for the manufacture of tetrahydrofuranylfentanyl. There is no information on the actual method(s) used for the production of tetrahydrofuranylfentanyl that has been detected in Europe to date.

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

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

([16]) Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.
([17]) The detailed description of the most common procedure, referred to as the 'Siegfried method', is readily available on the internet (see, for example, http://opioids.com/fentanyl/synthesis.html).
([18]) Self-educated clandestine chemists commented on the risk while discussing the synthesis of fentanyl and its potent 3-methyl and α-methyl homologues (comment was posted on 7 May, 2002); available at: https://the-hive.archive.erowid.org/forum/showflat.pl?Cat=&Number=260275 (Accessed: 27 June 2017).

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

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

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

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

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

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

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

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

Nineteen countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Spain, Sweden and the United Kingdom) reported that:

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

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

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

The EMA also reported that tetrahydrofuranylfentanyl:

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

5. Conclusion

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

Tetrahydrofuranylfentanyl has been available in the European Union since at least September 2016. It has been detected in one Member State where it has been seized as a liquid and a powder. The detected quantities are relatively small; however, they should be seen within the context of the high potency that is typical of the fentanils.

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

Fourteen deaths with confirmed exposure to tetrahydrofuranylfentanyl have been reported by one Member State. In at least 12 of the deaths, tetrahydrofuranylfentanyl was the cause of death or contributed to the death.

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

Tetrahydrofuranylfentanyl is under assessment within the United Nations system. It will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017. Currently, neither a critical review nor a written recommendation has been published. Tetrahydrofuranylfentanyl is not subject to control measures in 22 Member States and Turkey.

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

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

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

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EMCDDA, Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal
Tel. (351) 211 21 02 00 | info@emcdda.europa.eu
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