European Monitoring Centre
for Drugs and Drug Addiction

DRAFT

Technical report on *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (tetrahydrofuranylfentanyl; THF-F)

Parts of this technical report were prepared under contract from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Given the time frame stipulated in the Council Decision, additional data presented and discussed during the preparatory meeting for the risk assessment and the risk assessment meeting have not yet been incorporated into the technical report. In addition, this technical report has not been formally edited by the EMCDDA. As such, this report should be regarded as a draft document until such time that the final version is produced by the EMCDDA which will incorporate the additional data and which will be formally edited. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The *Risk assessment report on a new psychoactive substance: N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (tetrahydrofuranylfentanyl)* to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

3 November 2017

Annex 1 to the *Risk Assessment Report on N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (tetrahydrofuranylfentanyl).

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Introduction

In accordance with Article 5 of the *Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances* ([1]) on 25 April 2017, the EMCDDA and Europol launched the Joint Report procedure for *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (tetrahydrofuranylfentanyl) on the basis of data reported by the Member States to the European Union Early Warning System in accordance with Article 4 of the Council Decision. The information collection process for the Joint Report was completed in June 2017. The report was submitted to the EU Institutions in July 2017 (EMCDDA, 2017a). In accordance with Article 6 of the Council Decision, on 14 September 2017, the Council of the European Union requested that a risk assessment on tetrahydrofuranylfentanyl should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for the risk assessment, and, to facilitate the risk assessment process, the EMCDDA is responsible for the collection and analysis of data on the substance to be assessed as well as drafting a technical report. This technical report has been prepared for the risk assessment of tetrahydrofuranylfentanyl that will be held at the EMCDDA premises in Lisbon on Wednesday 8 November 2017.

Some of the sections in this report were prepared under EMCDDA contracts (ref. CT.17.SAT.0084.1.0 and CT.17.SAT.0110.1.0).

Data sources

The information in this technical report is derived from:

- data reported by the Member States, Turkey, and Norway to the EMCDDA and Europol in accordance with Council Decision 2005/387/JHA (EMCDDA, 2017a); and,

- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, online drug discussion forums and related websites, and online vendors selling tetrahydrofuranylfentanyl.

Search strategy

Literature searches used both chemical structure and text queries in online databases; searches were conducted in August 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 and substructure of tetrahydrofuranylfentanyl as well as a similarity search. Structural and text-based searches in SureChEMBL patent database retrieved no hits.

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

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

search terms used were: ‘tetrahydrofuranylfentanyl’, ‘tetrahydrofuranyl-fentanyl’, ‘tetrahydrofuranyl fentanyl’, ‘THF-F’, ‘fentanyl tetrahydrofuranyl analog’.

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.

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.

Note

It is important to note that when interpreting the information on self-reported user experiences in this report, it is not possible to confirm the specific substance(s) that have been claimed to be used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. Moreover, the actual composition of the substance/product may differ over time and different geographical areas. In addition, the information provided on user websites may not necessarily be representative of other users of tetrahydrofuranylfentanyl and should be regarded as illustrative only. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

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Acknowledgements

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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]oxolane-2-carboxamide (tetrahydrofuranylfentanyl) is a tetrahydrofuran-2-carboxamide derivative of *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) and structurally related to fentanyl, which is a propionamide (Table 1). Tetrahydrofuranylfentanyl contains one basic nitrogen atom in the piperidine ring and readily forms salts with organic or inorganic acids.

Tetrahydrofuranylfentanyl has one positional isomer, which is 3-tetrahydrofuranylfentanyl. In 3-tetrahydrofuranylfentanyl, the carboxamide is attached to the 3-position of the tetrahydrofuran ring ([5]).Tetrahydrofuranylfentanyl contains a stereogenic centre thus allowing for the existence of a pair of enantiomers, (*S*)-tetrahydrofuranylfentanyl and (*R*)-tetrahydrofuranylfentanyl. There is no information on the actual enantiomer found on the European drug market or whether it is the racemic mixture.

Until recently (Helander et al., 2017), information about tetrahydrofuranylfentanyl could not be identified in the scientific literature, which suggests that this compound appears to have no published history.

Tetrahydrofuranylfentanyl is a close structural relative of fentanyl ([6,7]), 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 pain management.

Tetrahydrofuranylfentanyl is the saturated derivative of furanylfentanyl ([8]) which was the subject of an EMCDDA–Europol Joint Report in January 2017 and risk-assessed under the auspices of the Scientific Committee of the EMCDDA in May 2017 (EMCDDA, 2017b). Tetrahydrofuranylfentanyl is also structurally related to acetylfentanyl and acryloylfentanyl, both of which were the subject of EMCDDA–Europol Joint Reports in December 2015 and November 2016, following reports of deaths in Europe. In February 2017, the risk assessment meeting on acryloylfentanyl (EMCDDA, 2017c) was convened. On 25 September 2017, the Council of the European Union decided that acryloylfentanyl should be subjected to control measures across the European Union (Council of the European Union, 2017).

([5]) Throughout this report, 'tetrahydrofuranylfentanyl' refers to 2-tetrahydrofuranylfentanyl.

([6]) http://www.emcdda.europe.eu/publications/drug-profiles/fentanyl

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

([8]) Tetrahydrofuranylfentanyl contains a tetrahydrofuran (aliphatic ring), whereas furanylfentanyl contains a furan (aromatic derivative of tetrahydrofuran). Furanylfentanyl might be used as a precursor for the synthesis of tetrahydrofuranylfentanyl; however, this has not been documented.

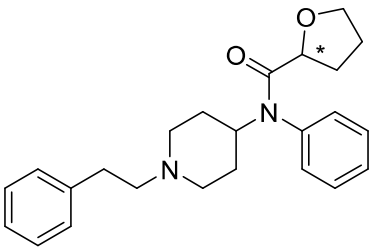
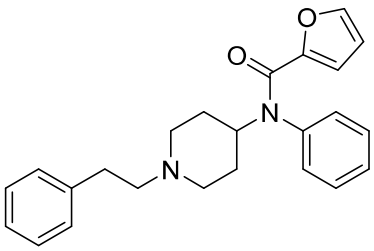
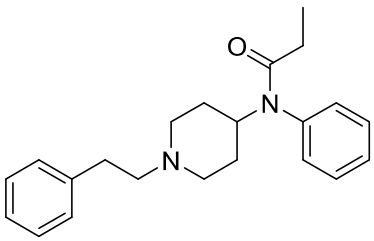
Tetrahydrofuranylfentanyl	Furanylfentanyl	Fentanyl
		
$C_{24}H_{30}N_2O_2$	$C_{24}H_{26}N_2O_2$	$C_{22}H_{28}N_2O$
378.52 g/mol	374.48 g/mol	336.48 g/mol

Figure 1: The molecular structure, molecular formula and molecular mass of tetrahydrofuranylfentanyl (left), furanylfentanyl (middle) and fentanyl (right). The asterisk denotes a chiral carbon.

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, acetylfentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, para-fluorofentanyl and thiofentanyl, are controlled under Schedule I and IV; alfentanil, butyrfentanyl, fentanyl, remifentanil and sufentanil are controlled under Schedule I. The controls on acetylfentanyl and butyrfentanyl entered into force in 2016 and 2017, respectively.

Names and other identifiers

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

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide

Chemical Abstract name:

2-Furancarboxamide, tetrahydro-*N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-

Other names:

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]tetrahydrofuran-2-carboxamide

N-(1-Phenethylpiperidin-4-yl)-*N*-phenyltetrahydrofuran-2-carboxamide

Chemical Abstract Service Registry Numbers (CAS RNs) ([9]):

Not registered

PubChem SID ([10])*:*

Not registered

IUPAC International Chemical Identifier Key (InCHI Key) ([11]):

OHJNHKUFSKAANI-UHFFFAOYSA-N

SMILES ([12]):

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

Common names:

Tetrahydrofuranylfentanyl; tetrahydrofuranfentanyl; tetrahydrofuran fentanyl; tetrahydrofuranyl fentanyl; tetrahydrofuran-fentanyl; THF-F

Street names:

THF-fentanyl; tetrahydrofuran-F; Tetra.

Identification and analytical profile

Physical description

Tetrahydrofuranylfentanyl hydrochloride has been described as a crystalline solid (Cayman Chemical Company, 2017) and the free base as a white powder (SWGDRUG, 2017). Tetrahydrofuranylfentanyl hydrochloride has been reported to be soluble in dichloromethane, methanol and water (Slovenian National Forensic Laboratory, 2017). 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, similar to fentanyl, is expected to be lipophilic ([13]). 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 C.

([9]) 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. Search conducted on 23 October 2017.

([10]) Search conducted on 23 October 2017 at https://pubchem.ncbi.nlm.nih.gov.

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

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

([13]) The respective calculated LogP values for tetrahydrofuranylfentanyl and fentanyl are 3.04 and 3.89 (ACD/ChemSketch 2015 release version, Advanced Chemistry Development Inc., Toronto, Canada). The respective LogP values calculated by StarDrop version 6.3.1 software (Optibrium Ltd, Cambridge, UK) for acryloylfentanyl and fentanyl are 4.18 and 3.89. The measured LogP value for fentanyl is 4.05 (Hansch et al., 1995).

Chemical stability and typical reactions

Specific information about tetrahydrofuranylfentanyl could not be identified. For long-term storage it is recommended that tetrahydrofuranylfentanyl, supplied as a solid, is stored at -20 °C (Cayman Chemical Company, 2017).

Analytical profile

Analytical data for tetrahydrofuranylfentanyl include: gas chromatography mass spectrometry (GC-MS), high performance liquid chromatography (high resolution) (tandem) mass spectrometry (LC-HRMS), Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR), proton nuclear magnetic resonance (^{1}H NMR) spectroscopy and gas chromatography condensed phase infrared spectroscopy and ion chromatography (GC- (MS)-IR) (Helander et al., 2017; Slovenian National Forensic Laboratory, 2017; SWGDRUG, 2017). Studies on the ability to differentiate between the 2- and 3-tetrahydrofuranylfentanyl isomers or enantiomers could not be identified ([14]).

It is possible that immunoassays for fentanyl may not detect or 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 using more suitable detection techniques, such as (tandem) mass spectrometry (Helander et al., 2017). Similarly, tetrahydrofuranylfentanyl is not expected to give a positive response to tests developed for morphine-type opioids.

Recently, a new bioassay-based method which relies on the activation of the μ-opioid receptor signalling pathway for the detection of synthetic opioids, including tetrahydrofuranylfentanyl, has been reported (Cannaert et al., 2017).

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 tetrahydrofuranylfentanyl that has been detected on the drug market in Europe. However, analysis of a collected sample of tetrahydrofuranylfentanyl that was test purchased from an online vendor apparently based in China also identified '4-aminophenyl-1-phenethylpiperidine', i.e. *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) (Slovenian National Forensic Laboratory, 2017), which is a commonly used precursor for synthesising many fentanyl analogues.

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

Synthesis

A synthesis procedure for tetrahydrofuranylfentanyl could not be identified in the literature. It is likely that its synthesis relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl and other fentanyl analogues. Accordingly, methods developed for the multistep synthesis of fentanyl are applicable to tetrahydrofuranylfentanyl but use a

([14]) 3-Tetrahydrofuranylfentanyl is also commercially available as a reference standard: https://www.caymanchem.com/product/22664

different acylating agent in the acylation of the appropriate 4-phenylaminopiperidine precursor. For example, the synthesis method of tetrahydrofuranylfentanyl could use 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 tetrahydrofuran-2-carbonyl chloride (Figure 2). As mentioned above, the detection of the 4-ANPP precursor was reported as part of the analysis of a test purchase product. The preparation of the 3-tetrahydrofuranylfentanyl isomer would be expected to involve the use of tetrahydrofuran-3-carbonyl chloride as the acylating agent. It has been demonstrated that *N*-(2-furoyl)piperazine could be directly reduced to *N*-(tetrahydro-2-furoyl)piperazine (Gluchowski et al., 2000) but whether this is applicable to the reduction of furanylfentanyl to tetrahydrofuranylfentanyl remains to be studied. If this were feasible then it would suggest that furanylfentanyl might serve as a precursor to tetrahydrofuranylfentanyl.

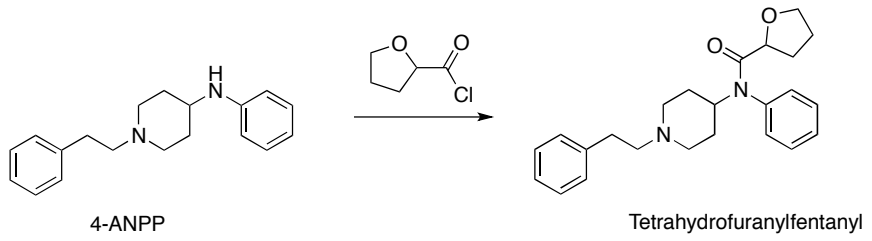


Figure 2. A possible step of the synthesis of tetrahydrofuranylfentanyl.

Most of these synthetic procedures are relatively straightforward. Due to the typical high potency of fentanils there is a risk of severe poisoning following accidental exposure during their manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substances. Likewise, accidental exposure to the fentanils could pose a 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. The antidote naloxone should be readily available to personnel in sufficient quantities; training in resuscitation, including the administration of naloxone, should also be available (IAB, 2017; US CDC, 2013; US CDC, 2016; US DEA, 2017b).

The 4-ANPP precursor, as well as *N*-phenethyl-4-piperidone (NPP, a pre-precursor), were scheduled in 2017 and are listed in Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (CND, 2017). The scheduling came into force on 18 October 2017 (INCB, 2017). In 2010, the U.S. Drug Enforcement Administration placed 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 illicit laboratories (US DEA, 2010). Other routes developed for the production of fentanyl may also be used for the manufacture of tetrahydrofuranylfentanyl. These methods have been reviewed (Soine, 1986; Carroll and Brine, 1989; Hsu and Banks, 1992; Fritschi and Klein, 1995; Yadav et al., 2010; Vardanyan and Hruby, 2014). To date, there is no information on the actual method(s) used for the production of tetrahydrofuranylfentanyl that has been detected on the European drug market.

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. A collected sample of tetrahydrofuranylfentanyl was reported to contain 4-ANPP (Slovenian National Forensic Laboratory, 2017), which, as mentioned above, is a commonly used precursor for synthesising many fentanils.

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA have noted that tetrahydrofuranylfentanyl has typically been detected in powders and liquids.

A1.3. Route of administration and dosage

As with other fentanils, tetrahydrofuranylfentanyl 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). Of note is that ready-to-use nasal sprays purportedly containing solutions of tetrahydrofuranylfentanyl have been offered by online vendors in Sweden. However, it is worth noting that some of these products are not always labelled and/or they may be sold as another substance. This finding extends to the use of other fentanils that have appeared in Europe in the past few years, including acryloylfentanyl (EMCDDA, 2017c; Ujváry et al., 2017) and furanylfentanyl (EMCDDA, 2017b).

Data reported to the EMCDDA regarding an acute intoxication with confirmed exposure to tetrahydrofuranylfentanyl noted that the substance was administered intra-nasally by nasal spray (Section D1.2).

Dosage

Limited information is available regarding the dose and the dose regimens of tetrahydrofuranylfentanyl. It is not possible to currently discern the 'typical' dosages administered by users. Doses appear to differ depending on factors such as the route of administration, the tolerance of the users, the use of other drugs, and the desired effects. Given the difficulties of collecting such data, it should be used with caution. Furthermore, the purity, amount and/or composition of the substance ingested are not typically known by the user. Moreover, the actual composition of the substance may differ over time and different geographical areas.

One comment made on a user forum suggested that, upon insufflation, tetrahydrofuranylfentanyl was 'active at 2 mg' and that 'up to over 10 mg seems comfortable' in a user who also used kratom ([15]) 'several times a week' ([16]).

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacologically, tetrahydrofuranylfentanyl is an opioid receptor agonist.

([15]) Kratom refers to the *M. speciosa* plant known to contain constituents (e.g. mitragynine) with opioid-like activity (Raffa, 2015).

([16]) https://drugs-forum.com/threads/tetrahydrofuranylfentanyl-info.295272/ (last accessed 07 September 2017).

Pharmacodynamics

In vitro studies

The currently available data suggests that tetrahydrofuranylfentanyl ([17]) binds to the μ-opioid receptor (MOR) with high selectivity (K_i = 0.95 nM) over the κ- and δ-opioid receptors (KOR and DOR) with K_i values of 741 nM and 1,730 nM, respectively (Table 1) ([18]) (US DEA, 2017a).

Table 1 provides a summary of additional binding and functional activity data that illustrate that tetrahydrofuranylfentanyl (EC_{50} = 89 nM, [^{35}S]GTPγS binding assay, E_{max} = 73.8%) functioned as a MOR agonist ([19]). In comparison, morphine (EC_{50} = 22.2 nM, [^{35}S]GTPγS binding assay, E_{max} = 81.0%) and fentanyl (EC_{50} = 15.2 nM, E_{max} = 90.4%) were approximately 4- and 6-times more potent than tetrahydrofuranylfentanyl and all three test drugs exhibited comparable efficacy under these *in vitro* conditions.

Table 1. Opioid receptor binding and functional activity data of tetrahydrofuranylfentanyl (THF-F)* (adapted and modified from US DEA, 2017a).

MOR	**THF-F**	**DAMGO**	**Morphine**	**Fentanyl**	**Naltrexone**
[^{3}H]DAMGO binding Ki (nM)	0.95 ± 0.32	0.252 ± 0.052	0.223 ± 0.051	0.056 ± 0.010	0.092 ± 0.017
IC_{50} (nM)	4.4 ± 1.5	–	–	–	–
[^{35}S]GTPγS binding	**THF-F**	**DAMGO**	**Morphine**	**Fentanyl**	
Stimulation EC_{50} (nM)	89 ± 16	15.2 ± 3.3	22.2 ± 2.8	15.2 ± 2.1	–
Maximal stimulation (%)*	73.8 ± 5.0	98.0 ± 4.1	81.0 ± 1.8	90.4 ± 2.2	–
DOR	**THF-F**	**DPDPE-OH**	**Morphine**	**Fentanyl**	**Naltrexone**
[^{3}H]DPDPE binding Ki (nM)	1,730 ± 260	2.77 ± 0.50	186 ± 13	249 ± 57	17.4 ± 4.8
IC_{50} (nM)	2,200 ± 300	–	–	–	–
[^{35}S]GTPγS binding	**THF-F**	**DPDPE-OH**	**Morphine**	**Fentanyl**	
Stimulation EC^{50} (nM)	1,440 ± 550	8.8 ± 2.1	566 ± 56	850 ± 140	–
Maximal stimulation (%)**	16.2 ± 3.7	99.53 ± 0.34	79.6 ± 5.5	62.1 ± 30	–
KOR	**THF-F**	**U-50,488H**	**Morphine**	**Fentanyl**	**Nor-BNI**

([17]) Isomeric composition not specified.

([18]) K_i represents the equilibrium inhibition constant for the test drug displacing the radioligand.

([19]) EC_{50} represents the concentration that causes a half-maximal response of the agonist.

[^{3}H]U-69,593 binding Ki (nM) IC_{50} (nM)	741 ± 44 1,720 ± 270	0.274 ± 0.063 –	30.2 ± 1.4 –	121 ± 11 –	0.38 ± 0.10 –
[^{35S}]GTPγS binding	**THF-F**	**U-50,488H**	**Morphine**	**Fentanyl**	
Stimulation EC_{50} (nM)	5,790 ± 430	1.62 ± 0.32	65 ± 19	700 ± 110	–
Maximal stimulation (%)**	62.1 ± 5.3	96.5 ± 7.7	73.2 ± 5.9	60.8 ± 8.5	–

* 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-N-Me-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. 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.

Tetrahydrofuranylfentanyl showed moderate affinity toward KOR (K_i = 741 nM) with low potency and moderate relative efficacy (EC_{50} = 5,790 nM, [^{35}S]GTPγS binding assay, E_{max} = 62.1%). As far as DOR was concerned, binding affinity, potency and efficacy were relatively low (K_i = 1,730 nM, EC_{50} = 1,440 nM, [^{35}S]GTPγS binding assay, E_{max} = 16.2%), which suggested a MOR selective profile, at least under these *in vitro* conditions. All test drugs used as positive control (Table 1) were shown to be efficacious agonists.

These *in vitro* studies have established tetrahydrofuranylfentanyl to be a MOR agonist. It is not known, however, to what extent this MOR agonist effect, which is responsible for causing respiratory depression (among other effects), would translate to high toxicity *in vivo*.

These data also indicated that saturation of the furanyl ring (also found in furanylfentanyl, subject of a recent risk assessment in May 2017 (EMCDDA, 2017b) led to a significant drop in potency, when investigated under identical *in vitro* conditions. For example, tetrahydrofuranylfentanyl displayed a 34-fold reduction in affinity (furanylfentanyl K_i = 0.0249 nM) and 35-fold drop in potency at MOR (furanylfentanyl EC_{50} = 2.52 nM, [^{35}S]GTPγS binding) although furanylfentanyl was found to be somewhat more efficacious relative to the MOR agonist DAMGO ([20]) (furanylfentanyl E_{max} = 55.5% vs. E_{max} = 73.8%, Table 1, see above) (EMCDDA, 2017b; US DEA, 2016b).

([20]) DAMGO: Tyr-Ala-Gly-*N*-Me-Phe-Gly-ol.

Animal studies

Results from animal studies could not be identified.

Pharmacokinetics

Apart from a recent conference abstract briefly discussing *in vitro* experiments with a series of fentanyl analogues, no *in vitro* or *in vivo* studies could be identified in the literature. According to this report (Wilde et al., 2017), in a human liver microsomal preparation the predominant metabolic step for tetrahydrofuranylfentanyl appears to be *N*-desalkylation, as in the case of fentanyl. Hydroxylation of the piperidine ring and the phenylethyl side chain, *N*-oxidation and amide hydrolysis to 4-ANPP were also observed.

The extent to which the biotransformation products are comparable to furanylfentanyl or other closely related analogues remains to be investigated. It seems likely that some overlap might exist, including the amide hydrolysis product 4-ANPP (Watanabe et al., 2017).

There is some information on the biological activity of 4-ANPP using intact guinea pig ileum preparations. Compared to fentanyl (IC_{50} = 4 nM), 4-ANPP was significantly less potent in inhibiting contractions of ileum segments induced by coaxial electrical stimulation (IC_{50} = 12,000 nM). The IC_{50} value determined for morphine was 50 nM (Schneider and Brune, 1986). Two metabolites showed activity in this study: the phenolic derivative hydroxylated at the 4-position of the phenylethyl moiety of fentanyl ([21]), the activity (IC_{50} = 240 nM) of which was found to lie between morphine and pethidine (IC_{50} = 1,300 nM), and the benzylic alcohol type derivative hydroxylated at the alpha-position, i.e. benzylic methylene, of the phenylethyl moiety of fentanyl which had an IC_{50} value of 50 nM.

One user described the 'high' obtained from insufflating an estimated ('eyeballed') of 20 mg of tetrahydrofuranylfentanyl to last for about 2 hours (route of administration ('insufflation') ([22]).

Inter-individual genetic variability in metabolising enzymes

Specific information about tetrahydrofuranylfentanyl could not be identified. For fentanyl, oxidative dealkylation by hepatic CYP3A4 and by CYP3A5 isoenzymes to norfentanyl has been demonstrated (Guitton et al., 1997, Jin et al., 2005, Labroo et al., 1997) The variation of the expression of the genes coding for these CYP3A isoenzymes among populations might be of clinical significance (Meyer and Maurer, 2011) but further studies are needed to examine the toxicological significance, if any, of such polymorphisms.

Interactions with other substances and other interactions

Specific information about tetrahydrofuranylfentanyl could not be identified, although it seems conceivable that interactions observed with fentanyl might equally apply (Preston, 2016). For example, should tetrahydrofuranylfentanyl 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,

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

([22]) https://drugs-forum.com/threads/tetrahydrofuranylfentanyl-info.295272/ (last accessed 07 September 2017).

nefazodone, ritonavir, saquinavir, suboxone, verapamil ([23]) may result in increased plasma concentration of tetrahydrofuranylfentanyl. This could increase the risk of poisoning, including potentially fatal respiratory depression.

The concomitant use of other central nervous system (CNS) depressants with tetrahydrofuranylfentanyl, such as other opioids, sedatives/hypnotics (such as the benzodiazepines and the z-drugs), ethanol, pregabalin, gabapentin, tranquillisers, and sedating anti-histamines, may produce additive depressant effects.

The use of fentanyl with serotoninergic 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 tetrahydrofuranylfentanyl.

Effects on ability to drive and operate machines

No studies of the effects of tetrahydrofuranylfentanyl 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 tetrahydrofuranylfentanyl.

A3. Psychological and behavioural effects

Information on the psychological and behavioural effects of tetrahydrofuranylfentanyl is limited. From the data available, it appears that the psychoactive profile of tetrahydrofuranylfentanyl might share at least some similarities with other opioid analgesics such as fentanyl and heroin ([24]).These would include relaxation and euphoria; at higher doses, sedation and profound intoxication may occur.

A4. Legitimate uses of the product

Tetrahydrofuranylfentanyl 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 tetrahydrofuranylfentanyl is used for other legitimate purposes.

There are no reported uses of tetrahydrofuranylfentanyl 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 for tetrahydrofuranylfentanyl returned no results.

([23]) For a more comprehensive list of drug interactions with fentanyl, see, for example, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&source=homeMedSearch&keyword=fentanyl&category=human&isNewQuery=true

([24]) One user described a 'Nice rush, high lasts about 2 hours, very clean and warm. Taking maybe (eyeballed) 20 mg within 2 hours caused intense nausea' https://drugs-forum.com/threads/tetrahydrofuranylfentanyl-info.295272/ (last accessed 07 September 2017).

There is no marketing authorisation (existing, on-going or suspended) for tetrahydrofuranylfentanyl neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency, which was undertaken as part of the Joint Report process (EMCDDA, 2017a).

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

B2. Human data

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

While no specific data exist for tetrahydrofuranylfentanyl, 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 tetrahydrofuranylfentanyl.

Section C. Prevalence of use

Information from seizures, collected and biological samples

Tetrahydrofuranylfentanyl was formally notified on 23 December 2016 by the EMCDDA on behalf of Sweden, in accordance with Article 4 of the Council Decision. The Reporting Form details a seizure of 22 millilitres of pale yellow liquid that was seized on 29 September 2016 by Swedish Police in Karlstad. The substance was analytically confirmed by GC-MS, liquid chromatography–high resolution mass spectrometry (LC–HRMS) and NMR by the Swedish National Forensic Centre.

Two Member States (Slovenia and Sweden) have reported detections of tetrahydrofuranylfentanyl ([25]) (EMCDDA, 2017a).

It is important to note that detections of tetrahydrofuranylfentanyl may be under-reported since the substance is not routinely screened for in Europe. Three Member States (Austria, Slovenia and

([25]) '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.).

Sweden) reported that tetrahydrofuranylfentanyl is part of routine screening in some, but not all, laboratories.

Information from seizures

In total, 53 seizures of tetrahydrofuranylfentanyl were reported to the EMCDDA and Europol. All of these were reported by Sweden. Of these, 26 seizures occurred in 2016, and the other 27 in the first 6 months of 2017.

A majority of the seizures were made by police at street-level (50 cases), with the remaining three seizures made by customs.

Physical forms seized included:

- liquids (48 seizures; amounting to a total volume of 950 millilitres of substance)
- powders (5 seizures; 99.4 grams)

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

Information from collected samples

Slovenia reported a sample of a brown powder which was purchased from an Internet vendor. The sample was apparently shipped from China and was received in August 2016. The precursor 4-ANPP was also detected in the sample.

Information from biological samples

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

Availability, supply, price

The available data suggests that tetrahydrofuranylfentanyl is sold online as a powder and as ready-to-use nasal sprays**.**

Information on production

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

Information on trafficking

No information was reported to the EMCDDA in relation to the trafficking of tetrahydrofuranylfentanyl. Information on the source of tetrahydrofuranylfentanyl is limited to one report regarding a test purchase of the substance. Here, the substance was ordered from an online vendor apparently based in China (see above).

Availability from Internet vendors

Tetrahydrofuranylfentanyl is sold on the surface web. Its availability on the darknet is not currently known. As mentioned above, a collected sample of the substance was ordered from an online vendor apparently based in China which supplied 5 grams.

In addition, two sites apparently based in Sweden offered tetrahydrofuranylfentanyl in liquid form as nasal sprays at claimed concentrations of 10 mg/ml and 13 mg/ml. The price of a 10 ml nasal spray (both concentrations) was EUR 51. The price for 25 ml was EUR 118 (for the 13 mg/ml solution).

Prevalence of use

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

Of additional note is that, in the past few years, fentanils have been sold in Europe as ready-to-use nasal sprays. In some cases they have also been sold as e-liquids for vaping. In general, these novel products could make it easier to use such substances (with similar effects to injecting) and make them more socially acceptable, potentially expanding their use in new user groups. These are new developments that will require careful monitoring. Nasal sprays claiming to contain tetrahydrofuranylfentanyl have been offered by online vendors within the European Union.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

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

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of tetrahydrofuranylfentanyl and/or its metabolites in humans. Although the pharmacology and toxicology of tetrahydrofuranylfentanyl remains largely unstudied, the available data suggests that the nature of its effects share some similarities with opioid analgesics such as morphine and fentanyl. The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, miosis, and respiratory depression or arrest. They also have an abuse liability and dependence potential (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; Romberg et al., 2003).

Similar to other opioid analgesics, the most serious acute health risk associated with tetrahydrofuranylfentanyl use is probably respiratory depression, which can lead to apnoea, respiratory arrest and death (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; White & 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).

Recent clinical and community experience in treating poisonings caused by fentanils suggests that larger than normal doses and repeated doses of naloxone may be required to manage the poisoning in some cases; longer periods of observation may also be required (Klar et al., 2016; Moss et al., 2017; Somerville et al., 2017; Sutter et al., 2017).

Data from serious adverse events associated with tetrahydrofuranylfentanyl are discussed below. Information from a single case of acute intoxication with confirmed exposure to tetrahydrofuranylfentanyl, suggests that the clinical features of poisoning may be similar to those found with fentanyl and other opioid analgesics. These include reduced level of consciousness or unconsciousness, respiratory depression and arrest, and miosis.

Acute intoxications reported by the Member States

A single case of acute intoxication with confirmed exposure to tetrahydrofuranylfentanyl was reported to the EMCDDA ([26]). The case occurred in Sweden in October 2016, and involved a 26 year old male who had administered 8 actuations of a 'fentanyl' nasal spray. The poisoning was classed as severe. The clinical features were consistent with the use of an opioid analgesic, and included reduced consciousness, respiratory depression and miosis. The patient was treated with 0.2 mg of naloxone (route of administration and response was not reported). The only other substance detected was flunitrazolam. The patient survived. This case has also been published in the literature (Helander et al., 2017).

Acute intoxications identified from other sources

Acute intoxications identified from other sources are limited to the case presented above (Helander et al., 2017).

Deaths reported by the Member States

A total of 14 deaths were reported by 1 Member State: Sweden. In all cases, exposure to tetrahydrofuranylfentanyl was analytically confirmed from post-mortem samples (femoral blood or muscle).

The deaths occurred between September 2016 and March 2017 with 8 occurring in 2016 and 6 in 2017.

Of these deaths, 8 were male (57%) and 6 were female (43%). The mean age of the males was 31 years (median 29) and ranged from 25 to 41 years; the mean age of the females was 32 years (median 30) and ranged from 29 to 38 years.

Circumstances and cause of death

In all but one case, the individuals were found dead (predominantly in a home environment). In all cases there was a lack of information regarding symptoms experienced by the deceased prior to death. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication).

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

The cause of death was reported in 13 out of 14 cases. In at least 12 deaths, intoxication with tetrahydrofuranylfentanyl was reported either as the primary cause of death or as likely to have contributed to death (even in presence of other substances); other substances were detected in all 14 cases.

Tetrahydrofuranylfentanyl was quantified in 5 cases. Post-mortem femoral blood concentrations ranged from 2 to 54 ng/g blood (median 18 ng/g blood). Due to the toxicity of opioids and variability in user tolerance, determination of a 'fatal' concentration based on a post-mortem blood concentration may not be reliable. In the majority of circumstances involving fentanils, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use.

A range of other substances were detected in the reported deaths, including: benzodiazepines, zopiclone, pregabalin, antidepressants, antipsychotics, antihistamines, synthetic cathinones, anticonvulsants and ethanol. Other opioids were detected in 3 of the deaths; tramadol, benzodioxolfentanyl and acryloylfentanyl.

Overall, whilst other substances may have contributed some toxicity, a synergistic effect with tetrahydrofuranylfentanyl would have been likely with other central nervous system depressants such as ethanol, benzodiazepines, opioids, etc. Nevertheless, the apparent fentanyl-like nature of tetrahydrofuranylfentanyl means that the primary toxic contribution could be attributed to the tetrahydrofuranylfentanyl and death may not have occurred if tetrahydrofuranylfentanyl had not been used. An assessment of the Toxicological Significance Score (TSS) (Elliott, Sedefov, & Evans-Brown, 2017) incorporating the above considerations showed that tetrahydrofuranylfentanyl had a TSS value of 3 (high) in 13 out of 14 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining death, an alternative pathological cause of death was cited (TSS value of 1, low).

Deaths identified from other sources

Since December 2016, at least 2 deaths associated with tetrahydrofuranylfentanyl have been reported in the United States. No further details are available on these cases (US DEA, 2017a).

D2. Chronic health effects

D2.1. Animal data

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

D2.2. Human data

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

D3. Factors affecting public health risks

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

Tetrahydrofuranylfentanyl is being sold on the surface web as a drug in its own right. It has been sold as a 'research chemical' in several physical forms, such as powders and ready-to-use nasal sprays.

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

Due to its relatively recent availability on the drug market, the availability of information, degree of knowledge and perceptions amongst users concerning tetrahydrofuranylfentanyl and its effects are limited.

D3.3. Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviours of users of tetrahydrofuranylfentanyl. Section C (above) and Section E6 (below) provides additional information on the likely user groups of tetrahydrofuranylfentanyl.

D3.4. Nature and extent of health consequences

Acute health risks

Although the pharmacology and toxicology of tetrahydrofuranylfentanyl remains largely unstudied, the available data suggests that the nature of its effects share some similarities with opioid analgesics such as morphine and fentanyl.

The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, and respiratory depression. They also have an abuse liability and dependence potential (Cox, 2011; Dahan et al., 2001; Pattinson, 2008).

Similar to other opioid analgesics, the most serious acute risk arising from the use of tetrahydrofuranylfentanyl is probably from respiratory depression, which can lead to apnoea, respiratory arrest, and death (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; White & Irvine, 1999).

In general, this risk may be exacerbated by:

- the difficulty in diluting/using fentanils (as they are typically highly potent), which can lead to a toxic dose being accidentally used (de Boer et al., 2003; Sutter et al., 2017);
- the apparent rapid onset of severe poisoning following use (Somerville et al., 2017);
- using routes of administration that allow large amounts of the substance to rapidly reach the central nervous system (such as injecting, insufflation, and inhalation) (Macleod et al., 2012);
- availability of easy to use dosage forms (such as nasal sprays and e-liquids);
- lack of awareness and experience of users with these new substances (effects and dosage);
- use of other central nervous system depressants (such as other opioids, benzodiazepines, and alcohol) (e.g. van der Schrier et al., 2017) ;
- lack of tolerance to opioids in opioid-naïve persons (such as new or former users);
- use in environments where it may be difficult to summon help in the event of poisoning (e.g. alone in a home environment) (Somerville et al., 2017);
- limited availability of the antidote naloxone in community settings (EMCDDA, 2015; EMCDDA, 2016; Somerville et al., 2017).

In addition, and, often unknown to users, the fentanils are sold as heroin or mixed with heroin. They are also used to make counterfeits of highly sought-after analgesics and benzodiazepines. They have also been sold in or as drugs such as cocaine (Klar et al., 2016; SFDPH, 2015; Sutter et al., 2017; Tomassoni et al., 2017). Due to this, users may not be aware that they are using a fentanil; in some cases these individuals will have no tolerance to opioids nor access to community naloxone programmes. Overall, these factors may increase the risk of life-threatening poisoning.

Given the above risks, poisonings by fentanils may manifest as outbreaks which have the potential to overwhelm emergency responders and other local healthcare systems (Klar et al., 2016; SFDPH, 2015; Sutter et al., 2017; Tomassoni et al., 2017).

Accidental exposure to the fentanils may also pose a risk to non-users, including family and friends, law enforcement and emergency responders. Such risks may need to be assessed so that, where required, appropriate procedures, training and environmental and personal protective measures can be provided for handling materials suspected to contain these substances (IAB, 2017; US CDC, 2016; Moss et al., 2017; US DEA, 2017a). Any required responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole & Nelson, 2017; Lynch, Suyama, & Guyette, 2017).

Managing 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 manage the poisoning in some cases, longer periods of observation may also be required (Klar et al., 2016; Moss et al., 2017; Somerville et al., 2017; Sutter et al., 2017). This may reflect, among other factors, the high potency of the fentanils, their half-lives, the dose an individual is exposed to, and, the relatively short half-life of naloxone.

Chronic health risks

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

D3.5. Long-term consequences of use

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

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

There is limited data on the conditions which tetrahydrofuranylfentanyl is obtained and used. Tetrahydrofuranylfentanyl is offered for sale on the surface web, typically as powders and ready-to-use nasal sprays.

Section E. Social Risks

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

E1. Individual social risks

There is no information on the individual social risks that may be associated with the use of tetrahydrofuranylfentanyl. Given that tetrahydrofuranylfentanyl appears to act as an opioid analgesic, any such risks may have some similarities with those associated with illicit opioids. These may negatively impact on education or career, family or other personal and social relationships and may result in marginalisation.

E2. Possible effects on direct social environment

There is no information on the possible effects of tetrahydrofuranylfentanyl on the direct social environment. Given that tetrahydrofuranylfentanyl appears to act as an opioid analgesic, any such effects may have some similarities with those associated with the use of illicit opioids.

E3. Possible effects on society as a whole

There is no specific information on the possible effects of tetrahydrofuranylfentanyl on society as a whole.

As discussed above, accidental exposure to the fentanils may pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel as well as 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 managing poisoning, including in resuscitation and adequate provision of naloxone to reverse poisoning. Any required responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole & Nelson, 2017; Lynch, Suyama, & Guyette, 2017).

E4. Economic costs

There are no data on the health and social costs related to tetrahydrofuranylfentanyl.

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

There are no data on the possible effects of tetrahydrofuranylfentanyl related to the cultural context.

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

While no specific examples are available on the possible appeal of tetrahydrofuranylfentanyl to specific user groups (aside from psychonauts), it is reasonable to assume tetrahydrofuranylfentanyl may be sought by those looking for 'legal' substitutes for illicit opioids, such as heroin and/or prescription opioids.

As discussed above, the open sale of solutions of fentanils in novel dosage forms—such as ready-to-use nasal sprays and e-liquids for vaping—poses additional concerns. These novel forms have the potential to make the use of fentanils easier (with similar effects to injecting) and more socially acceptable.

Section F. Involvement of organised crime

F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain

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

Slovenia reported a collected sample of tetrahydrofuranylfentanyl to Europol and the EMCDDA where the country of origin was reported as China ([27]).

The seizure of an illicit laboratory producing fentanils in Europe in 2013 (EMCDDA, 2017b) suggests that the capability to manufacture fentanils may exist within the European Union.

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

No information was reported nor identified concerning the impact of tetrahydrofuranylfentanyl 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 was reported nor identified concerning evidence of the same groups of people being involved in different types of crime related to the availability of tetrahydrofuranylfentanyl.

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

No information was reported nor identified concerning incidents of violence related to the availability of tetrahydrofuranylfentanyl.

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

No information was reported nor identified concerning evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society related to the availability of tetrahydrofuranylfentanyl.

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

No information was reported nor identified concerning the economic costs and consequences related to the availability of tetrahydrofuranylfentanyl.

F7. Use of violence between or within criminal groups

No information was reported nor identified concerning the use of violence between or within criminal groups related to the availability of tetrahydrofuranylfentanyl.

([27]) The sample also contained 4-aminophenyl-1-phenethylpiperidine (4-ANPP), a precursor that can be used for the synthesis of fentanyl and many fentanil analogues.

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

No information was reported nor identified concerning evidence of strategies to prevent prosecution related to the availability of tetrahydrofuranylfentanyl.

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European Monitoring Centre
for Drugs and Drug Addiction

Annex 2. List of participants at the risk assessment meetings of *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (tetrahydrofuranylfentanyl)

7-8 November 2017

A. Extended Scientific Committee

Dr Anne Line BRETTEVILLE-JENSEN
Norwegian Institute for Alcohol and Drug Research, Oslo
Chair of the Scientific Committee

Professor Dr Gerhard BUEHRINGER
Addiction Research Unit, Department of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Institut für Therapieforschung (IFT), Munich

Professor Dr Paul DARGAN
Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

Dr Marina DAVOLI
Department of Epidemiology, Lazio Regional Health Service, Rome

Professor Dr Gabriele FISCHER
Medical University Vienna, Center of Public Health, Vienna

Professor Dr Henk GARRETSEN
Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg

Professor Dr Krzysztof KRAJEWSKI
Department of Criminology, Jagiellonian University, Krakow

Dr Fernando RODRÍGUEZ de FONSECA
Fundación IMABIS, Hospital Universitario Carlos Haya de Málaga, Málaga

Professor Dr Rainer SPANAGEL
Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Dr Wim BEST
Utrecht University, Faculty of Science, Freudenthal Institute, Utrech

Dr Simon BRANDT
School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Professor Dr Gaetano Di CHIARA
Biomedical Sciences Department, University of Cagliari, Cagliari

Professor Dr Éva KELLER
Semmelweis University, Department of Forensic and Insurance Medicine, Budapest

Dr Claude GUILLOU
Directorate F – Health, Consumers and Reference Materials, DG Joint Research Centre, European Commission

Edith HOFER
Organised Crime and Drugs Policy Unit, DG HOME, European Commission

Dr Leon Van Aerts
Section Pharmacology, Toxicology and Biotechnology, College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht, on behalf of European Medicines Agency

Werner VERBRUGGEN
Europol's Drug Unit, Europol

Paul GRIFFITHS
Scientific Director, EMCDDA

Dr Roumen SEDEFOV
Head of Unit, Supply reduction and new drugs unit, EMCDDA

B. Invited Experts

Professor Dr Volker AUWÄRTER
Freiburg University, Institute of Forensic Medicine, Freiburg

Dr Robert KRONSTRAND
Dep. Forensic Genetics and Toxicology, Swedish National Board of Forensic Medicine, Linköping

Professor Dr Bela SZABO
Institute of Experimental and Clinical Pharmacology and Toxicology, Freiburg

Dr István UJVÁRY
Budapest University of Technology and Economics, Budapest

C. EMCDDA Staff

Anabela ALMEIDA
Action on new drugs sector, Supply reduction and new drugs unit

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