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

ANNEX

Risk assessment report on a new psychoactive substance:
***N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide**
(tetrahydrofuranylfentanyl; THF-F)

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

Contents

1. Introduction

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (commonly known as tetrahydrofuranylfentanyl). The report is intended for policy makers and decision makers in the institutions of the European Union.

The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines ([1]). It is written as a stand-alone document, which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on tetrahydrofuranylfentanyl, is provided below.

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ([2]) (hereafter 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'EU Early Warning System' ([3])) that may pose public health and social threats, including those related to the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances ([4]) that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ([5]).

([1]) EMCDDA (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/html.cfm/index100978EN.html

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

([3]) The information exchange mechanism laid down by the Council Decision is operationalized as the *European Union Early Warning System on New Psychoactive Substances ('EU Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Reitox National Focal Points and Europol National Units in the Member States, the European Commission, and the European Medicines Agency.

([4]) According to the definition provided by the Council Decision, a 'new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; 'new narcotic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

([5]) In compliance with the provisions of the United Nations Single Convention on Narcotic Drugs, 1961, and the United Nations Convention on Psychotropic Substances, 1971.

Tetrahydrofuranylfentanyl was formally notified on 23 December 2016 by the EMCDDA on behalf of the Swedish National Focal Point, in accordance with Article 4 of the Council Decision. The notification related to the seizure of 22 millilitres of pale yellow liquid seized on 29 September 2016 by police. Following an assessment of the available information on tetrahydrofuranylfentanyl, and, in accordance with Article 5 of the Council Decision, on 3 July 2017 the EMCDDA and Europol submitted a *Joint Report* on tetrahydrofuranylfentanyl ([6]) to the Council of the European Union, the European Commission, and the European Medicines Agency (EMA). Taking into account the conclusion of the *Joint Report*, and, in accordance with Article 6 of the Council Decision, on 14 September 2017 the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of tetrahydrofuranylfentanyl was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of four additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of tetrahydrofuranylfentanyl, including health and social risks. A further four experts participated in the risk assessment: two experts from the Commission, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 8 November 2017 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol, and the EMA. A list of the extended Scientific Committee, as well as the list of other participants attending the risk assessment meeting, is annexed to this report (Annex 2).

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

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

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

Finally, it is important to note that this risk assessment report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with tetrahydrofuranylfentanyl. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify, and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. The EMCDDA's toxicovigilance system, which is a central component of the EU Early Warning System, has also been strengthened resulting in more information being available regarding serious adverse events associated with new psychoactive substances. Nonetheless, it is likely that these events remain under-detected and under-reported.

2. Physical, chemical and pharmacological description

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (tetrahydrofuranylfentanyl or THF-F) is structurally related to fentanyl, which is a propionamide. Tetrahydrofuranylfentanyl contains one basic nitrogen atom in the piperidine ring and readily forms salts with organic or inorganic acids. Fentanyl analogues (fentanils) have in common an aralkyl group attached to a 4-*N*-acylanilinopiperidine.

Until 2017, information about tetrahydrofuranylfentanyl could not be identified in the scientific literature, which suggests that this compound has no published history. Tetrahydrofuranylfentanyl is the saturated derivative of furanylfentanyl which was risk-assessed by the Scientific Committee of the EMCDDA in May 2017.

Pharmacologically, tetrahydrofuranylfentanyl is an opioid receptor agonist.

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

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

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

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

Tetrahydrofuranylfentanyl as free base or as its hydrochloride salt may occur as solids. Due to its similarity to fentanyl, the free base could be expected to be sparingly soluble in water; whereas its hydrochloride and citrate salt is expected to have greater aqueous solubility; the free base is expected to be lipophilic.

In Europe, tetrahydrofuranylfentanyl has been seized as powder and in liquid solutions. In the latter case the available data suggests that tetrahydrofuranylfentanyl is sold online on the surface web as ready to use nasal sprays.

The analytical identification of tetrahydrofuranylfentanyl in physical and biological samples is possible using several analytical techniques. These include chromatographic and mass-spectrometric techniques. Routine commercially available immunoassays may not detect this compound.

Analytical reference materials are important for the correct identification and for facilitating the quantification of tetrahydrofuranylfentanyl in physical and biological samples. Such reference materials are commercially available. It should be noted that concentrations in blood samples can be in the sub-nanogram per millilitre range.

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

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).

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.

Pharmacology

Currently available data on the pharmacodynamics of tetrahydrofuranylfentanyl are limited to studies investigating its binding and functional activity at opioid receptors *in vitro*. These data show that tetrahydrofuranylfentanyl is a highly selective μ-opioid receptor agonist *in vitro*, and that it is less potent than morphine and fentanyl.

A recent study indicates that the metabolic pathway of tetrahydrofuranylfentanyl shares some similarities with fentanyl. Consequently drug-drug interactions observed with fentanyl might equally apply.

The concomitant use of other central nervous system (CNS) depressants, including other opioids, sedatives/hypnotics, ethanol, pregabalin, gabapentin, tranquillisers, and sedating anti-histamines, may produce additive depressant effects.

Psychological and behavioural effects

From the available data, the psychological and behavioural effects of tetrahydrofuranylfentanyl may share some similarities with fentanyl and other opioid analgesics. These would include relaxation and euphoria; at higher doses, sedation and profound intoxication may occur.

Legitimate uses

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 available CAS Registry Numbers returned no hits.

There is no marketing authorisation (existing, on-going, or suspended) for tetrahydrofuranylfentanyl in the European Union or in the Member States that responded to the request for information that was undertaken as part of the Joint Report process ([6]).

There is no information to suggest that tetrahydrofuranylfentanyl is currently used in the manufacture of a medicinal product in the European Union ([6]). 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.

3. Chemical precursors that are used for the manufacture

Information on the chemical precursors and the synthetic methods employed for tetrahydrofuranylfentanyl detected on the drug market within the European Union is limited. 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), which is a commonly used precursor for synthesising many fentanyl analogues.

A synthesis procedure for tetrahydrofuranylfentanyl could not be identified in the literature; however the manufacture of tetrahydrofuranylfentanyl most likely relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl. Accordingly, methods developed for the synthesis of fentanyl are applicable to tetrahydrofuranylfentanyl. Most of these are straightforward, make use of common laboratory equipment and precursors, and require only basic knowledge of chemistry. The substances 4-ANPP and tetrahydrofuran-2-carbonyl chloride could be used for the manufacture of the substance. It has been demonstrated that *N*-(2-furoyl)piperazine could be directly reduced to *N*-(tetrahydro-2-furoyl)piperazine, 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.

Two potential precursors of tetrahydrofuranylfentanyl and other fentanils, 4-ANPP as well as *N*-phenethyl-4-piperidone (NPP, a pre-precursor), have been recently scheduled ([7]).

Tetrahydrofuranylfentanyl poses a risk of poisoning if accidental exposure occurs during its manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substance.

4. Health risks

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of tetrahydrofuranylfentanyl, as well as its dependence potential, and its similarities to and differences from other chemically or pharmacologically related substances.

It is important to note that when interpreting the information from acute intoxications and deaths reported to the EMCDDA as well as information from user websites, that individuals may have used other substances in addition to tetrahydrofuranylfentanyl. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the reported effects.

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

While specific information for tetrahydrofuranylfentanyl is limited, of note is the apparent popularity of selling ready-to-use or using homemade nasal sprays containing solutions for the administration of fentanils. These typically contain milligram amounts of dissolved substance. The preparation of such solutions is inherently prone to mistakes in weighing and dilution which may lead to solutions with higher (or lower) concentrations. This may constitute an increased risk of acute toxicity to the individuals, who are unlikely to be able to control the dose of fentanil being consumed.

In addition, recent seizures in Europe of nasal sprays containing other fentanils found that these have been sold in some cases as unlabelled bottles. In other cases, users have also filled nasal sprays previously containing medicines (such as nasal decongestants) with fentanils. The lack of labelling increases the potential for accidental use by others and therefore poses a risk of poisoning.

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

Acute toxicity

The acute toxicity of tetrahydrofuranylfentanyl and/or its metabolites has not been studied in non-clinical and clinical studies.

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.

While there is limited data on the clinical features of poisoning caused by tetrahydrofuranylfentanyl, they are likely to include reduced level of consciousness or unconsciousness, respiratory depression and arrest, and miosis. Similar to other opioid analgesics, the most serious acute risk arising from the use of tetrahydrofuranylfentanyl is probably respiratory depression, which can lead to apnoea, respiratory arrest, and death.

The timely administration of the antidote naloxone should reverse acute poisoning caused by tetrahydrofuranylfentanyl. Recent clinical and community experience in treating poisonings caused by fentanils suggests that larger than normal doses and repeated doses of naloxone may be required to manage the poisoning in some cases; longer periods of observation may also be required.

In general for fentanils, the risk of life-threatening poisoning may be exacerbated by: the difficulty in diluting/using fentanils (as they are typically highly potent), which can lead to a toxic dose being accidentally used; the apparent rapid onset of severe poisoning following use; using routes of administration that allow large amounts of the substance to rapidly reach the central nervous system (such as injecting, insufflation, and inhalation); availability of easy to use dosage forms (such as nasal sprays and e-liquids); lack of awareness and experience of users with these new substances (effects and dosage); use of other central nervous system depressants (such as other opioids, benzodiazepines, and alcohol); 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); and, limited availability of the antidote naloxone in community settings.

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. Due to this, users may not be aware that they are using a fentanil; in some cases these individuals will have no tolerance to opioids nor access to community naloxone programmes. Overall, these factors may increase the risk of life-threatening poisoning.

Acute intoxications

A single case of acute intoxication with confirmed exposure to tetrahydrofuranylfentanyl was reported to the EMCDDA. The case occurred in Sweden 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.

Deaths

A total of 14 deaths were reported by 1 Member State: Sweden. In all cases, 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.

Cause of death and toxicological significance

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 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). For a number of reasons, including 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) ([8]) 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).

Circumstances 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).

Ability to operate machinery and drive

There have been no studies of the effects of tetrahydrofuranylfentanyl on the ability to drive and operate machines. However, it is well established that opioid narcotic analgesics, such as fentanyl, impair the mental and physical ability required to drive and operate machines. This effect is likely to extend to tetrahydrofuranylfentanyl.

Chronic toxicity

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

([8]) Elliott, S., Sedefov, R. and Evans-Brown, M. (2017), 'Assessing the toxicological significance of new psychoactive substances in fatalities', Drug Testing and Analysis. https://doi.org/10.1002/dta.2225

Abuse liability and dependence potential

There have been no studies that have investigated the abuse liability and dependence potential of tetrahydrofuranylfentanyl. Given what is currently known about its pharmacology, including some similarities to other fentanils and opioid narcotic analgesics, it may have a potential for abuse and dependence. Further research will be required in order to determine such effects.

Public health risks

The public health risks associated with tetrahydrofuranylfentanyl may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences. Detailed information, including data on sporadic versus chronic use, that allow for a determination of public health risks associated with tetrahydrofuranylfentanyl are not available. In addition, risk of accidental exposure needs to be considered.

Extent, frequency, and patterns 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.

Tetrahydrofuranylfentanyl appears to be sold online in small and wholesale amounts as powders and ready-to-use nasal sprays (sometimes as a 'research chemical').

Availability and quality on the market

A total of 53 seizures have been reported by one Member State, 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), as liquids (48 seizures) and powders (5 seizures).

It is important to note that detections of tetrahydrofuranylfentanyl may be under-reported since the substance is not routinely screened for.

Nasal sprays claiming to contain tetrahydrofuranylfentanyl have been offered by online vendors within the European Union. The availability of tetrahydrofuranylfentanyl on the darknet is not currently known.

Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviours of users of tetrahydrofuranylfentanyl. While no specific examples are available on the possible appeal of the substance to specific user groups (aside from psychonauts), it is reasonable to assume that it may may be sought by those looking for ‘legal’ substitutes for illicit opioids, such as heroin and/or prescription opioids.

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

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

Nature and extent of health consequences

In addition to the individual health risks that are discussed above, there are some further considerations related to the fentanils as a group that should be considered in respect to potential risks to public health.

Mirroring the increased availability of fentanils on the drug market over the past few, there has also been an increase in the number of outbreaks of mass poisoning caused by fentanils, particularly in the United States and Canada. These types of outbreaks have had the potential to overwhelm emergency responders and other local healthcare systems, as well as deplete stocks of naloxone. Stocks and availability of the naloxone, as well as adequacy of training in how to resuscitate poisoned patients both in clinical and community settings may need to be assessed. This might also include a review of the availability of naloxone to users through take-home naloxone programmes.

As noted, new dosage forms—such as ready-to-use nasal sprays and e-liquids for vaping—along with open sales on the surface web and darknet marketplaces add to the complexity of the problem caused by the fentanils. They have become easier to get hold of and easier to use. The Committee is concerned about whether the availability of ‘novel’ dosage forms has the potential to make the use of fentanils more socially acceptable.

An additional challenge in respect to reducing risk in users and potential users is the balance between providing information to prevent harm and the unintended consequences of communicating the risks of opioids. There is evidence that using terms to describe them as 'potent', 'strong', 'deadly', and 'toxic' can lead some individuals to specifically seek out these substances. Such unintended promotion of the substances may also extend to former users and other groups.

Adding to these challenges is evidence from Europe, the United States, and Canada that fentanils are being sold to unsuspecting users in/as heroin, counterfeit medicines (including commonly used opioid analgesics and benzodiazepines), cocaine, and other illicit drugs. As users will be unaware of this, it increases the risk of severe and fatal poisoning in both opioid users and especially other groups who may have no existing tolerance to opioids. Non-opioid users are unlikely to be aware of these risks and are unlikely to have access to community opioid overdose prevention programmes, including take-home naloxone programmes.

Accidental exposure to fentanils may also pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those in custodial settings and postal services. Where necessary, specific risks should be identified and assessed, and, appropriate measures to reduce these risks should be implemented. This may include appropriate protective equipment, training in resuscitation, and making naloxone readily available to relevant personnel in sufficient quantities in the event of poisonings. Any required measures should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose.

Long-term consequences of use

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

Conditions under which the substance is obtained and used

There is limited information on the conditions which tetrahydrofuranylfentanyl is obtained and used. Tetrahydrofuranylfentanyl appears to be sold on the surface web, typically as ready-to-use nasal sprays.

Overall, tetrahydrofuranylfentanyl may be deliberately sought after by some users; others, such as those that purchase it at street-level, may be unaware that they are using the substance which presents an inherent risk to the individuals.

5. 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 seen with opioids such as fentanyl and heroin.

Individual social risks

There is no information on whether the use of tetrahydrofuranylfentanyl causes individual social risks; however, any such risks may have some similarities with those associated with the use of illicit opioids, including fentanyl. These may impact on education or career, family or other personal and social relationships and may result in marginalisation.

Possible effects on direct social environment (e.g. neglect of family, violence)

There is no information on the possible effects of tetrahydrofuranylfentanyl on the direct social environment; however, any such risks may have some similarities with those associated with the use of illicit opioids.

Possible effects on society as a whole (public order and safety, acquisitive crime)

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

As discussed above, accidental exposure of fentanils may pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those in custodial settings and postal services.

Economic costs

There are no data on the effects of tetrahydrofuranylfentanyl in respect to its health and social costs.

Possible appeal to specific population groups

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

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

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

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

Slovenia reported a collected sample of tetrahydrofuranylfentanyl to Europol and the EMCDDA where the country of origin was reported as China ([9]).

The seizure of an illicit laboratory producing fentanils in Europe in 2013 suggests that the capability to manufacture fentanils may exist within the European Union.

7. Information on any assessment in the United Nations system

The World Health Organization (WHO) is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971. In May 2017, the WHO informed the EMCDDA that tetrahydrofuranylfentanyl will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017.

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

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

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

- In Latvia, tetrahydrofuranylfentanyl is included in the Cabinet Regulation N 847 'Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be Controlled in Latvia' and the law 'On the Procedures for the Coming into force and Application of the Criminal Law'.

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

- In Sweden, tetrahydrofuranylfentanyl is regulated under the Act on the Prohibition of Certain Goods Dangerous to Health, as of 25 January 2017.

([9]) 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.

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

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

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

- In Belgium, tetrahydrofuranylfentanyl is controlled by way of generic definition.

- In Poland, tetrahydrofuranylfentanyl is controlled according to the general definition of the 'substitute drug' (Act of 8 October 2010 amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection, Journal of Laws "Dz.U." No. 213, item 1396). Pursuant to Article 44b of the Act on counteracting drug addiction, it is prohibited to manufacture and introduce substitute drugs to trade.

Norway reported that tetrahydrofuranylfentanyl is controlled under medicines legislation.

Nineteen Member States (Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany ([10]), Greece, Hungary ([10]), Ireland, Italy, 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.

9. Options for control and the possible consequences of the control measures

Under Article 9.1 of the Council Decision, the option for control that is available at European Union level is for the Member States to submit the new psychoactive substance tetrahydrofuranylfentanyl to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the Single Convention on Narcotic Drugs, 1961.

([10]) As part of the Joint Report process, it was reported by the German and Hungarian National Focal Points that tetrahydrofuranylfentanyl is not controlled in Germany and Hungary, respectively (6). However, during the risk assessment meeting, two experts who were present informed that the substance is controlled under specific new psychoactive substances control legislation, by way of generic definition. As such, the control of the substance has been reflected in the totals that are presented in the conclusion.

There are no studies on the possible consequences of such control measures on tetrahydrofuranylfentanyl. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of tetrahydrofuranylfentanyl and hence the further expansion of the current open trade in this substance.

- A health consequence that might result from this control option is the benefit brought about by the presumed reduction in availability and use.

- This control option could facilitate the detection, seizure and monitoring of tetrahydrofuranylfentanyl related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies across the European Union.

- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement, and the courts.

- This control option could lead to replacement with other (established or new) psychoactive substances, which may in themselves have public health consequences and social risks.

- This control option could create an illicit market in tetrahydrofuranylfentanyl with the increased risk of associated criminal activity, including the involvement of organised crime.

- This control option could impact on both the quality/purity and price of any tetrahydrofuranylfentanyl still available on the illicit market. The extent to which this will impact on public health, criminality, or levels of use, is difficult to predict.

- It is difficult to predict the impact of this control option on current or future research by the pharmaceutical or chemical industries.

- In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of tetrahydrofuranylfentanyl on the market post-control, should this control option be pursued.

- Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include restricting the importation and supply of the substance as some Member States have already done.

10. Conclusion

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

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.

Tetrahydrofuranylfentanyl has been available in Europe since at least September 2016 and has been seized in 1 Member State (Sweden). Fourteen deaths have been reported by Sweden where exposure to tetrahydrofuranylfentanyl was confirmed. In many of cases, other drugs were also detected with tetrahydrofuranylfentanyl. In at least 12 of the deaths, tetrahydrofuranylfentanyl was reported to be either the cause of death or to have contributed to death.

It is likely that naloxone works as an antidote to poisoning caused by tetrahydrofuranylfentanyl.

It is important to note that detections of tetrahydrofuranylfentanyl may be under-reported since the substance is not routinely screened for. Routine commercially available immunoassays may not detect this compound.

Tetrahydrofuranylfentanyl appears to be sold online typically as a liquid (as a ‘research chemical’).

Typically, the substance has been administered by nasal spray. Particular concerns exist over novel ways of administering fentanils including tetrahydrofuranylfentanyl. These include nasal sprays and e-liquids for vaping. These may have the potential to make the use of fentanils easier and more socially acceptable.

While no specific examples are available on the possible appeal of tetrahydrofuranylfentanyl to specific user groups, it can be assumed that it may be available to and being used by high-risk drug users, including opioid users.

Accidental exposure to tetrahydrofuranylfentanyl, as well as to other fentanils, may pose a risk to law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as to those in custodial settings and postal services. Where necessary, specific risks and appropriate measures to reduce these risks should be identified and implemented. Any required measures should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose.

There is no information regarding the involvement of organised crime in the manufacture, distribution (trafficking) and supply within the European Union. There is limited information on the chemical precursors and the synthetic routes used to manufacture the tetrahydrofuranylfentanyl detected within the European Union. Most of the synthetic routes are straightforward, make use of common laboratory equipment and readily available precursors, and require only basic knowledge of chemistry.

Information from seizures suggests that some tetrahydrofuranylfentanyl on the market in Europe has been produced by chemical companies based in China.

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

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

Five Member States control tetrahydrofuranylfentanyl under drug control legislation. Five Member States and Norway control tetrahydrofuranylfentanyl under other legislation.

As for any new psychoactive substance, many of the questions related to tetrahydrofuranylfentanyl that are posed by the lack of data on the risks to individual health, risks to public health, and social risks, could be answered through further research. Areas where additional information would be important include studies on: rationale for use, prevalence and patterns of use (including studies that examine user groups and risk behaviours); the market; chemical profiling; complete pharmacological profiling; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between tetrahydrofuranylfentanyl and other substances; the dependence and abuse potential; and the public health risks associated with its use.

The Committee notes that a decision to control tetrahydrofuranylfentanyl has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks and consequences arising from the use of tetrahydrofuranylfentanyl. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, since tetrahydrofuranylfentanyl was first detected at least nine new fentanils and a number of other new opioids that may replace it are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation.

Finally the Committee notes that it is important to continue to collect and disseminate accurate information on tetrahydrofuranylfentanyl to users, practitioners, policy makers, decision makers and those who may be at risk of accidental exposure. An additional challenge in respect to reducing risk in users and potential users is the balance between providing information to prevent harm and the unintended consequences of communicating the risks of opioids. There is evidence that using terms to describe them as 'potent', 'strong', 'deadly', and 'toxic' can lead some individuals to specifically seek out these substances. Such unintended promotion of the substances may also extend to former users and other groups.

11. List of annexes

Annex 1: Technical report on *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide (tetrahydrofuranylfentanyl).

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

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).

Table of contents

Introduction

In accordance with Article 5 of the *Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances* ([11]) on 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.

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

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 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.

Reported prepared by

Simon Brandt ([12]), Simon Elliott ([13]), Michael Evans-Brown ([14]), Helgi Valur Danielsson ([4]), Anabela Almeida ([4]), Rita Jorge ([4]), Rachel Christie ([4]), Sofía Sola ([4]), Ana Gallegos ([4]), and Roumen Sedefov ([4]).

Acknowledgements

The EMCDDA would like to extend their sincere thanks and appreciation to: the Early Warning System (EWS) correspondents of the Reitox national focal points and experts from their national early warning system networks; the Europol national units and Europol Project Synergy; and, Dr István Ujváry, iKem BT, Budapest, Hungary for reviewing some of the sections of this report.

([12]) School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, United Kingdom.
([13]) Alere Forensics, Malvern, Worcestershire, United Kingdom.
([14]) European Monitoring Centre for Drugs and Drug Addiction.

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

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 ([15]).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 ([16,17]), 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 ([18]) 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).

([15]) Throughout this report, 'tetrahydrofuranylfentanyl' refers to 2-tetrahydrofuranylfentanyl.
([16]) http://www.emcdda.europe.eu/publications/drug-profiles/fentanyl
([17]) Fentanyl is included in Schedule I of the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol.
([18]) 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.

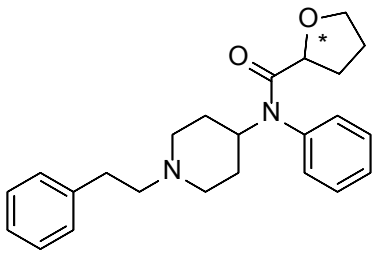
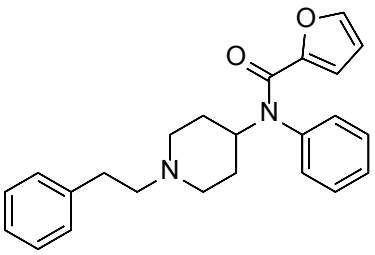
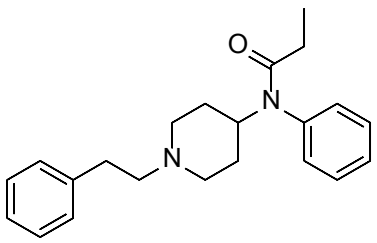
Tetrahydrofuranylfentanyl	Furanylfentanyl	Fentanyl
		
$C_{24}H_{30}N_2O_2$	$C_{24}H_{26}N_2O_2$	$C_{22}H_{28}N_2O$
378.52 g/mol	374.48 g/mol	336.48 g/mol

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) ([19]):

Not registered

PubChem SID ([20])*:*

Not registered

IUPAC International Chemical Identifier Key (InCHI Key) ([21]):

OHJNHKUFSKAANI-UHFFFAOYSA-N

SMILES ([22]):

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.

([19]) 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.
([20]) Search conducted on 23 October 2017 at https://pubchem.ncbi.nlm.nih.gov.
([21]) InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.
([22]) The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

Identification and analytical profile

Physical description

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 ([23]). 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.

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 ([24]).

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).

([23]) 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).

([24]) 3-Tetrahydrofuranylfentanyl is also commercially available as a reference standard: https://www.caymanchem.com/product/22664

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 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.

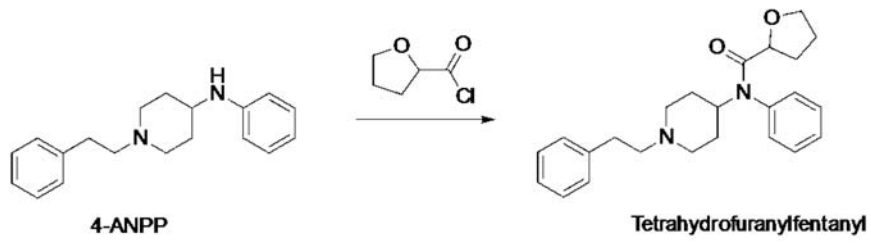


Figure 2. A possible step of the synthesis of tetrahydrofuranylfentanyl.

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 ([25]) 'several times a week' ([26]).

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacologically, tetrahydrofuranylfentanyl is an opioid receptor agonist.

Pharmacodynamics

In vitro studies

The currently available data suggests that tetrahydrofuranylfentanyl ([27]) 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) ([28]) (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 ([29]). 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.

([25]) Kratom refers to the *M. speciosa* plant known to contain constituents (e.g. mitragynine) with opioid-like activity (Raffa, 2015).
([26]) https://drugs-forum.com/threads/tetrahydrofuranylfentanyl-info.295272/ (last accessed 07 September 2017).
([27]) Isomeric composition not specified.
([28]) K_i represents the equilibrium inhibition constant for the test drug displacing the radioligand.
([29]) EC_{50} represents the concentration that causes a half-maximal response of the agonist.

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**
[^{3}H]U-69,593 binding Ki (nM)	741 ± 44	0.274 ± 0.063	30.2 ± 1.4	121 ± 11	0.38 ± 0.10
IC_{50} (nM)	1,720 ± 270	–	–	–	–
[35^S]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 [35^S]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 ([30]) (furanylfentanyl E_{max} = 55.5% vs. E_{max} = 73.8%, Table 1, see above) (EMCDDA, 2017b; US DEA, 2016b).

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 ([31]), 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.

([30]) DAMGO: Tyr-Ala-Gly-*N*-Me-Phe-Gly-ol.
([31]) Systematic name: *N*-{1-[2-(4-hydroxyphenyl)ethyl]piperidin-4-yl}-*N*-phenylpropionamide.

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') ([32]).

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, nefazodone, ritonavir, saquinavir, suboxone, verapamil ([33]) 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.

(32) https://drugs-forum.com/threads/tetrahydrofuranylfentanyl-info.295272/ (last accessed 07 September 2017).
(33) 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

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 ([34]).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.

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.

(34) 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).

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 ([35]) (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 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.

(35) ‘ 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.).

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 ([36]). 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).

([36]) 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 ([37]).

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.

([37]) 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.

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.

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, Utrecht

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

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

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

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

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

Dr 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

Rachel CHRISTIE
Action on new drugs sector, Supply reduction and new drugs unit

Michael EVANS-BROWN
Action on new drugs sector, Supply reduction and new drugs unit

Ana GALLEGOS
Action on new drugs sector, Supply reduction and new drugs unit

Rita JORGE
Action on new drugs sector, Supply reduction and new drugs unit

Joanna DE MORAIS
Action on new drugs sector, Supply reduction and new drugs unit

Sofía SOLA
Action on new drugs sector, Supply reduction and new drugs unit