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4F-iBF

Report on the risk assessment of *N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl) piperidin-4-yl]propanamide in the framework of the Council Decision on new psychoactive substances

About this series

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

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

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

Contents

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- the Early Warning System (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
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Foreword

This publication presents the data and findings of the risk assessment on the new psychoactive substance 4-fluoroisobutyrylfentanyl (4F-iBF) (*N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide), carried out by the extended Scientific Committee of the EMCDDA on 7 and 8 November 2017.

The Risk Assessment Report, which was submitted to the European Commission and the Council of the European Union on 14 November 2017, examines the health and social risks of the substance, information on international trafficking and the involvement of organised crime, as well as a consideration of the potential implications of subjecting the substance to control measures. 4-Fluoroisobutyrylfentanyl is the nineteenth new psychoactive substance to be risk assessed under the terms of Council Decision 2005/387/JHA.

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

In March 2018, at its 61st regular session, the Commission on Narcotic Drugs (CND) decided to place 4-fluoroisobutyrylfentanyl in Schedule I of the Single Convention on Narcotic Drugs of 1961 based on a recommendation by the World Health Organization. This recommendation was substantially supported by European data provided by the EMCDDA.

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

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

Dr Anne Line Bretteville-Jensen
Chair, Scientific Committee of the EMCDDA

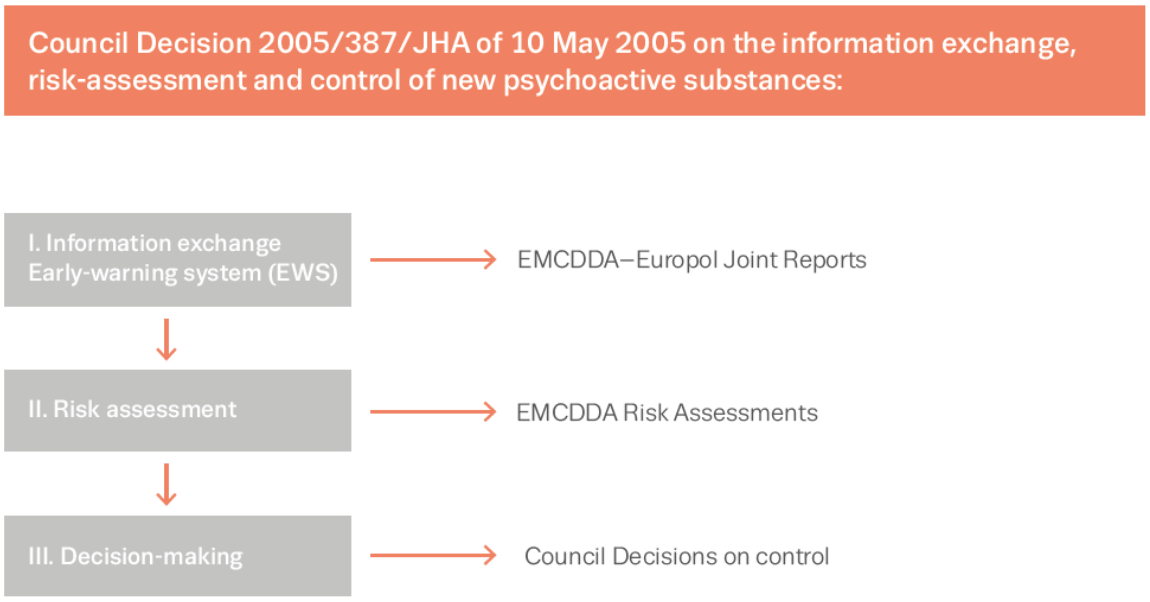
Alexis Goosdeel
Director, EMCDDA

EMCDDA actions on monitoring and responding to new drugs

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

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

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



Europol–EMCDDA Joint Report on 4F-iBF (*N*-(4 fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide) — a summary

Europol–EMCDDA Joint Report on a new psychoactive substance: *N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide — in accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

In March 2017, the EMCDDA and Europol examined the available information on a new psychoactive substance *N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide, commonly known by the abbreviation 4-fluoroisobutyrylfentanyl (4F-iBF), through a joint assessment based upon the following criteria: (1) the amount of the material seized; (2) evidence of organised crime involvement; (3) evidence of international trafficking; (4) analogy with better-studied compounds; (5) evidence of the potential for further (rapid) spread; and (6) evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information available on 4-fluoroisobutyrylfentanyl satisfied criteria 4 and 6. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report on 4-fluoroisobutyrylfentanyl as stipulated by Article 5.1 of the Decision. Accordingly, the NFPs, the Europol national units (ENUs), the EMA and the World Health Organization (WHO) were formally asked to provide the relevant information within six weeks from the date of the request, i.e. by 6 June 2017.

The resulting Joint Report on 4-fluoroisobutyrylfentanyl was submitted to the Council, the Commission and the EMA on 3 July 2017. The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in 4-fluoroisobutyrylfentanyl, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA.

The full text of the Joint Report can be found at:
www.emcdda.europa.eu/publications/joint-reports/4f-ibf

Risk Assessment Report on a new psychoactive substance: *N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl; 4F-iBF)

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*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (commonly known as 4-fluoroisobutyrylfentanyl). 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 4-fluoroisobutyrylfentanyl, 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

([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.

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]).

4-Fluoroisobutyrylfentanyl was formally notified on 26 August 2016 by the EMCDDA on behalf of the Slovenian national focal point, in accordance with Article 4 of the Council Decision. The notification related to the collected sample of 5 grams of white powder that was test-purchased as part of the EU co-funded RESPONSE project. Following an assessment of the available information on 4-fluoroisobutyrylfentanyl, and, in accordance with Article 5 of the Council Decision, on 3 July 2017 the EMCDDA and Europol submitted a *Joint Report* on 4-fluoroisobutyrylfentanyl ([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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl, 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 (page 52).

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

- Technical report on *N*-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl) (Annex 1);
- EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide (4-fluoroisobutyrylfentanyl) ([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,

([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.

([6]) EMCDDA (2017), EMCDDA–Europol Joint Report on a new psychoactive substance *N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide (4-fluoroisobutyrylfentanyl), EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/publications/joint-reports/4F-iBF

- Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ([2]).

Finally, it is important to note that this risk assessment report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with 4-fluoroisobutyrylfentanyl. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify, and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. The EMCDDA's toxicovigilance system, which is a central component of the EU Early Warning System, has also been strengthened resulting in more information being available regarding serious adverse events associated with new psychoactive substances. Nonetheless, it is likely that these events remain under-detected and under-reported.

Physical, chemical and pharmacological description

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl or 4F-iBF) is structurally related to fentanyl, which is a propionamide. 4-Fluoroisobutyrylfentanyl 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.

4-Fluoroisobutyrylfentanyl is known from the scientific literature. 4-Fluoroisobutyrylfentanyl is the positional isomer of 4-fluorobutyrfentanyl (4F-BF) and thus both substances are structurally very closely related, which results in the same molecular formula and molecular mass.

Pharmacologically, 4-fluoroisobutyrylfentanyl 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.

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

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

The major pharmacological effects of the fentanils, including their analgesic activity, are due to their activation of opioid receptors, and, in particular, the μ-opioid receptor. Besides their analgesic properties, a notable feature associated with μ-opioid receptor agonists is that they cause dose-dependent respiratory depression, 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.

4-Fluoroisobutyrylfentanyl 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; the hydrochloride and citrate salt could be expected to have greater aqueous solubility; and the free base is expected to be lipophilic.

In Europe, 4-fluoroisobutyrylfentanyl has been seized as a powder, tablet and as a liquid. It has been offered online as ready to use nasal sprays.

The analytical identification of 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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, 4-fluoroisobutyrylfentanyl 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). There are also instances where 4-fluoroisobutyrylfentanyl is advertised for sale in the form of blotters by Internet vendors. Users have also described rectal administrations.

From the limited data available it is not possible to discern the ‘typical’ dosages administered by users. While a range of doses have been reported, these appear to differ depending on factors such as the route of administration, the tolerance of the users, the use of other drugs, and the desired effects.

Pharmacology

Currently available data on the pharmacodynamics of 4-fluoroisobutyrylfentanyl are limited to studies investigating its binding and functional activity at opioid receptors *in vitro*, and its analgesic properties in mice. The *in vitro* data show that 4-fluoroisobutyrylfentanyl is a highly selective μ-opioid receptor agonist and that it is several times less potent than morphine and fentanyl. When the agonist activity of 4-fluoroisobutyrylfentanyl is compared with that of morphine, its potency over morphine is higher in tests *in vivo* (analgesia) than in tests *in vitro* (e.g., binding affinity for μ receptors). Its analgesic potency is almost ten times of that reported for morphine.

The pharmacokinetic properties of 4-fluoroisobutyrylfentanyl are consistent with the high lipophilicity of fentanyl derivatives that results in rapid absorption and tissue distribution, including diffusion across the blood-brain barrier.

Recent studies indicate the metabolic pathway of 4-fluoroisobutyrylfentanyl shares some similarities with other fentanils. 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 4-fluoroisobutyrylfentanyl 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

4-Fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl is used for other legitimate purposes.

There are no reported uses of 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl is currently used in the manufacture of a medicinal product.

Chemical precursors that are used for the manufacture

Information on the chemical precursors and the synthetic methods employed for 4-fluoroisobutyrylfentanyl detected on the drug market within the European Union is limited.

The manufacture of 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl. Most of these are straightforward, make use of common laboratory equipment and precursors, and require only basic knowledge of chemistry. The substances *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine and isobutyryl chloride and/or isobutyric anhydride could be used for the manufacture of the substance. A potentially detectable impurity might be predicted to include *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine. Use of a different acylating agent in the final acylation step could provide other fentanils.

A potential pre-precursor for 4-fluoroisobutyrylfentanyl and other fentanils, *N*-phenethyl-4-piperidone (NPP), has been recently scheduled ([7]).

4-Fluoroisobutyrylfentanyl 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.

Health risks

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of 4-fluoroisobutyrylfentanyl, 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 deaths reported to the EMCDDA as well as information from user websites, that individuals may have used other substances in addition to 4-fluoroisobutyrylfentanyl. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the reported effects.

While specific information for 4-fluoroisobutyrylfentanyl 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.

4-Fluoroisobutyrylfentanyl may be used in combination with other drugs (intentionally or unintentionally).

Limited data from seizures and collected samples have shown that 4-fluoroisobutyrylfentanyl has been detected in mixtures containing other opioids such as heroin and furanylfentanyl. The overall significance of these seizures is unclear; however, the identification of heroin in the seizures suggests that 4-fluoroisobutyrylfentanyl is being supplied through the illicit heroin market.

Acute toxicity

The acute toxicity of 4-fluoroisobutyrylfentanyl and/or its metabolites has not been studied in non-clinical and clinical studies.

Although the pharmacology and toxicology of 4-fluoroisobutyrylfentanyl largely remains unstudied, the available data suggests that the nature of its effects share some similarities with opioid analgesics

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

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 4-fluoroisobutyrylfentanyl, features of poisoning 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl. 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, 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

No acute intoxications with confirmed exposure to 4-fluoroisobutyrylfentanyl were reported to the EMCDDA.

Deaths

A total of 20 deaths were reported by 2 Member States: Sweden (16) and the United Kingdom (4). Exposure to 4-fluoroisobutyrylfentanyl was analytically confirmed in post-mortem samples in all cases from Sweden; no reference standard was available to distinguish between 4-fluoroisobutyrylfentanyl and 4-fluorobutyrylfentanyl in cases from the United Kingdom.

The deaths occurred between July 2016 and March 2017, with 17 occurring in 2016 and 3 in 2017. Of the 18 deaths where demographic data were available, 16 were male (80%) and 2 were female (20%). The mean age of the males was 35 years (median 34) and ranged from 20 to 52 years; the age of the females was 24 and 36 years.

Cause of death and toxicological significance

The cause of death was reported in 16 out of 20 cases. In at least 13 deaths, intoxication with 4-fluoroisobutyrylfentanyl 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 19 cases.

Post-mortem femoral blood concentrations of 4-fluoroisobutyrylfentanyl were quantified in 15 cases, and ranged from 0.76 to 370 ng/g blood (median 44 ng/g blood). In 2 cases, although the concentration was measured (44 and 85 ng/mL), it was not possible to determine if it related to 4-fluoroisobutyrylfentanyl or 4-fluorobutyrylfentanyl. For a number of reasons, including variability in user tolerance, determination of a 'fatal' concentration based on a post-mortem blood concentration is not 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 deaths, including: cannabinoids, benzodiazepines, amphetamine, zopiclone, zolpidem, pregabalin, gabapentin, antidepressants, antipsychotics, antihistamines, a synthetic cathinone (alpha-PHP), ketamine, and ethanol (alcohol). Other opiates/opioids were detected in 9 of the deaths: codeine, buprenorphine, tramadol, methadone, oxycodone, fentanyl, despropionylfentanyl, tetrahydrofuranylfentanyl, and acryloylfentanyl.

Overall, whilst other substances may have contributed some toxicity, a synergistic effect with 4-fluoroisobutyrylfentanyl would have been likely with other central nervous system depressants such as ethanol, benzodiazepines, opioids, etc. Nevertheless, the potent opioid nature of 4-fluoroisobutyrylfentanyl means that the primary toxic contribution could be attributed to 4-fluoroisobutyrylfentanyl and death may not have occurred if 4-fluoroisobutyrylfentanyl had not been used. An assessment of the toxicological significance score (TSS) ([8]) incorporating the above considerations shows that 4-fluoroisobutyrylfentanyl had a TSS value of 3 (high) in 15 out of 16 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 cause of death (drowning) was cited (TSS value of 1, low). The 4 cases where 4-fluoroisobutyrylfentanyl could not be unequivocally confirmed were not part of the assessment.

Circumstances of death

In the majority of cases there was a lack of information regarding any symptoms experienced by the deceased prior to death, but, where described in a few cases, the deceased had become unconscious and in one case the deceased was found convulsing. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's). Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

Deaths from other sources

In addition to deaths reported by the EMCDDA, more than 60 deaths with confirmed exposure to 4-fluoroisobutyrylfentanyl have recently been reported in the United States.

([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

Ability to operate machinery and drive

There have been no studies of the effects of 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl.

Chronic toxicity

No studies were identified that investigated the chronic health effects of 4-fluoroisobutyrylfentanyl and/or its metabolites.

Abuse liability and dependence potential

There have been no studies that have investigated the abuse liability and dependence potential of 4-fluoroisobutyrylfentanyl. 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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.

4-Fluoroisobutyrylfentanyl appears to be sold online in small and wholesale amounts as powders, liquids, and blotters (sometimes as a ‘research chemical’). 4-Fluoroisobutyrylfentanyl may also be sold on the illicit opioid market, as suggested by seizures where it was found in mixtures with other opioids such as heroin and furanylfentanyl. In these cases, it is reasonable to assume that these individuals will not be aware that they are consuming 4-fluoroisobutyrylfentanyl.

Availability and quality on the market

A total of 24 seizures have been reported by 4 Member States. The majority of the seizures took place in 2016, with a smaller number reported in 2017. 4-Fluoroisobutyrylfentanyl has been typically seized as a powder (9 seizures; total of 378.6 g), in tablet form (12 seizures; 6727 tablets), and as a liquid (3 seizures; total of 208 ml).

It is important to note that detections of 4-fluoroisobutyrylfentanyl may be under-reported since the substance is not routinely screened for.

Powders, liquids, and blotters claiming to contain 4-fluoroisobutyrylfentanyl have been offered by online vendors apparently based within the European Union.

The availability of 4-fluoroisobutyrylfentanyl on the darknet is not currently known.

Characteristics and behaviour of users

While no specific examples are available on the possible appeal of 4-fluoroisobutyrylfentanyl to user groups (aside from psychonauts), it is reasonable to assume that the substance 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 4-fluoroisobutyrylfentanyl is used in the home environment. In the majority of the deaths the individuals were found dead, often in a home environment. It appears that in at least some of these cases the poisoning with of 4-fluoroisobutyrylfentanyl was so severe that they were unable to call for help. Polydrug use, including the use of other central nervous system depressants such as opioids, was common in the deaths.

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 years, 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 4-fluoroisobutyrylfentanyl.

Conditions under which the substance is obtained and used

There is limited information on the conditions which 4-fluoroisobutyrylfentanyl is obtained and used. The substance is offered for sale on the surface web as a powder, liquids, and blotters.

4-Fluoroisobutyrylfentanyl has also been seized as tablets.

Information from a seizure case in the United Kingdom suggests that 4-fluoroisobutyrylfentanyl has been sold on the illicit opioid market in mixtures with heroin.

Overall, 4-fluoroisobutyrylfentanyl 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.

Social risks

While there have been no studies on the social risks of 4-fluoroisobutyrylfentanyl, 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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.

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 4-fluoroisobutyrylfentanyl.

Slovenia reported a collected sample of 4-fluoroisobutyrylfentanyl to both Europol and the EMCDDA where the country of origin was indicated as China. Belgium reported a seizure of 4-fluoroisobutyrylfentanyl to the EMCCDA where the final destination was Germany.

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.

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 4-fluoroisobutyrylfentanyl will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017.

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

Seven Member States (Cyprus, Estonia, France, Latvia, Lithuania, Sweden, and the United Kingdom) reported that 4-fluoroisobutyrylfentanyl is controlled under drug control legislation.

- In Cyprus, 4-fluoroisobutyrylfentanyl is controlled as a Class A drug within the Narcotic Drugs and Psychotropic Substances Law 1977.
- In Estonia 4-fluoroisobutyrylfentanyl is controlled by way of generic definition.
- In France, 4-fluoroisobutyrylfentanyl is controlled as of 5 September 2017.
- In Latvia, 4-fluoroisobutyrylfentanyl 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, 4-fluoroisobutyrylfentanyl is subjected to control measures by The Republic of Lithuania Minister of Health Order No V-22 (06/01/2017) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000'.
- In Sweden, 4-fluoroisobutyrylfentanyl is regulated under the Act on the Prohibition of Certain Goods Dangerous to Health, as of 25 January 2017.
- In the United Kingdom, 4-fluoroisobutyrylfentanyl is controlled under the Misuse of Drugs Act 1971 by way of a generic definition.

Three Member States (Austria, Belgium, and Poland) reported that 4-fluoroisobutyrylfentanyl is controlled under specific new psychoactive substances control legislation.

- In Austria, 4-fluoroisobutyrylfentanyl is covered by the phenethylamine generic definition within the Austrian Act on New Psychoactive substances.
- In Belgium, 4-fluoroisobutyrylfentanyl is controlled by way of generic definition.
- In Poland, 4-fluoroisobutyrylfentanyl 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.

Seventeen Member States (Bulgaria, Croatia, Czech Republic, Denmark, Finland, Germany ([9]), Greece, Hungary ([9]), Ireland, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovenia, and Spain), Turkey and Norway reported that 4-fluoroisobutyrylfentanyl is not subject to control measures at the national level.

Slovakia did not provide information on the control status of 4-fluoroisobutyrylfentanyl.

([9]) As part of the Joint Report process, it was reported by the German and Hungarian national focal points that 4-fluoroisobutyrylfentanyl 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.

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 4-fluoroisobutyrylfentanyl 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.

There are no studies on the possible consequences of such control measures on 4-fluoroisobutyrylfentanyl. 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl on the market post-control, should this control option be pursued.
- Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include restricting the importation and supply of the substance as some Member States have already done.

Conclusion

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl) 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 4-fluoroisobutyrylfentanyl is a narcotic opioid analgesic similar to fentanyl.

Similar to other opioid analgesics, the most serious acute risk arising from the use of 4-fluoroisobutyrylfentanyl is probably from respiratory depression, which can lead to apnoea, respiratory arrest, and death.

4-Fluoroisobutyrylfentanyl has been available in Europe since at least August 2016 and has been seized in 4 Member States. Sixteen deaths have been reported by 1 Member State where exposure to 4-fluoroisobutyrylfentanyl was confirmed. In many of cases, other drugs were also detected with 4-fluoroisobutyrylfentanyl. In at least 13 of the deaths, 4-fluoroisobutyrylfentanyl was reported to be either the cause of death or to have contributed to death. There have also been reports of deaths from the United States with confirmed exposure to the substance.

It is likely that naloxone works as an antidote to poisoning caused by 4-fluoroisobutyrylfentanyl.

It is important to note that detections of 4-fluoroisobutyrylfentanyl may be under-reported since the substance is not routinely screened for. Routine commercially available immunoassays may not detect this compound.

4-Fluoroisobutyrylfentanyl is sold online as a ‘research chemical’, typically as a powder and as ready-to-use nasal sprays, in small and wholesale amounts. Limited information from seizures suggests that 4-fluoroisobutyrylfentanyl may have also been sold on the illicit opioid market.

The substance can be administered by nasal spray, by nasal insufflation and orally. Other routes of administration, including injecting, and vaping of e-liquids have also been reported for fentanils. Particular concerns exist over novel ways of administering fentanils including 4-fluoroisobutyrylfentanyl. 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.

Information from police seizures as well as investigations into deaths indicates that 4-fluoroisobutyrylfentanyl is available to and being used by high-risk drug users, including opioid users.

Accidental exposure to 4-fluoroisobutyrylfentanyl, 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. However, given the fact that it has been detected in heroin samples the involvement of organised crime cannot be excluded. There is limited information on the chemical precursors and the synthetic routes used to manufacture the 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl on the market in Europe has been produced by chemical companies based in China.

4-Fluoroisobutyrylfentanyl has no recognised human or veterinary medical use in the European Union, nor, it appears, elsewhere. There are no indications that 4-fluoroisobutyrylfentanyl may be used for any other purpose aside from as an analytical reference standard and in scientific research.

4-Fluoroisobutyrylfentanyl is not listed for control in the Single Convention on Narcotic Drugs, 1961, nor in the Convention on Psychotropic Substances, 1971. 4-Fluoroisobutyrylfentanyl is currently under assessment by the United Nations system.

Seven Member States control 4-fluoroisobutyrylfentanyl under drug control legislation. Five Member States control 4-fluoroisobutyrylfentanyl under other legislation.

As for any new psychoactive substance, many of the questions related to 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, since 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl to users, practitioners, policy makers, decision makers, and those who may be at risk of accidental exposure. An additional challenge in respect to reducing risk in users and potential users is the balance between providing information to prevent harm and the unintended consequences of communicating the risks of opioids. There is evidence that using terms to describe them as 'potent', 'strong', 'deadly', and 'toxic' can lead some individuals to specifically seek out these substances. Such unintended promotion of the substances may also extend to former users and other groups.

ANNEX 1

Technical report on *N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl; 4F-iBF)

Introduction

In accordance with Article 5 of the *Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances* ([1]) on 25 April 2017, the EMCDDA and Europol launched the Joint Report procedure for *N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl) 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 Institutions of the European Union 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 4-fluoroisobutyrylfentanyl should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for a 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 4-fluoroisobutyrylfentanyl 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 the Council Decision (EMCDDA, 2017a); and,
- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, Internet drug discussion forums and related websites, and online vendors selling 4-fluoroisobutyrylfentanyl.

Search strategy

Literature searches used both chemical structure and text queries in online databases; searches were conducted in October 2017. The retrieved publications were then reviewed for additional relevant references (snowballing technique).

Chemical structure-based searches were done in SciFinder® (American Chemical Society, Chemical Abstract Service) and Reaxys® (Elsevier) databases using both the exact structure of 4-

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

fluoroisobutyrylfentanyl and a similarity search. Structural and text-based searches in the SureChEMBL patent database retrieved only one, though irrelevant, hit ([2]).

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), Web of Science™ (Thomson Reuters), and in popular English-language drug forums. The search terms used were: '4-fluoroisobutyrylfentanyl', '4-fluoro-isobutyrylfentanyl', '4-fluoro-isobutyrfentanyl', '4-fluoro-isobutrylfentanyl', '*para*-fluoroisobutyrylfentanyl', 4-F-iBF, 4-FiBF, 4-FIBF, FIBF, p-FIBF and p-FiBF.

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

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

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

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 4F-iBF and should be regarded as illustrative only. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

Report prepared by

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Acknowledgements

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([2]) A recent US patent mentions '*p*-fluoroisobutyrfentanyl' as one of the opioids against which a novel nasal naloxone spray formulation can be applied (Keegan et al., 2017).
([3]) School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, United Kingdom.
([4]) Alere Forensics, Malvern, Worcestershire, United Kingdom.
([5]) 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

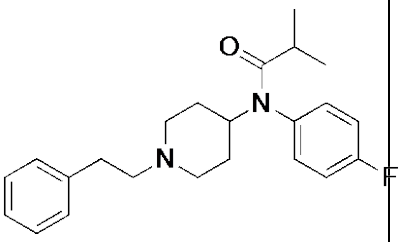
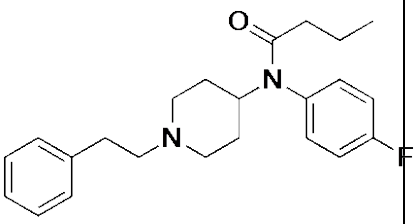
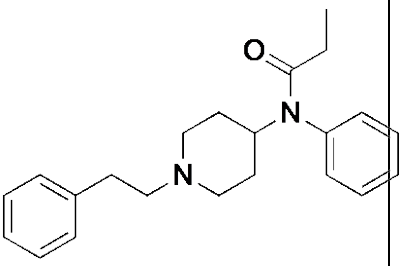
N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl) is structurally related to fentanyl, which is a fast and short-acting synthetic opioid that has been widely used in clinical practice as an adjunct to general anaesthesia during surgery and for postoperative pain management. 4-Fluoroisobutyrylfentanyl contains one basic nitrogen atom in the piperidine ring readily forming salts with organic or inorganic acids.

4-Fluoroisobutyrylfentanyl is also structurally related to acetylfentanyl, acryloylfentanyl, and furanylfentanyl, which were the subjects of EMCDDA–Europol Joint Reports submitted in December 2015, November 2016 and January 2017, respectively, following reports of deaths in Europe (EMCDDA, 2016a; EMCDDA, 2017b; EMCDDA, 2017c). In February 2017 and May 2017, risk assessment meetings on acryloylfentanyl (EMCDDA, 2017d) and furanylfentanyl (EMCDDA, 2017e) were convened under the auspices of the Scientific Committee of the EMCDDA following the request by the Council of the European Union. On 25 September 2017, the Council of the European Union decided that acryloylfentanyl should be subjected to control measures across the European Union (CEU, 2017).

4-Fluoroisobutyrylfentanyl differs from fentanyl by the presence of a fluorine atom on the anilido phenyl ring and the presence of an isobutyramide group in place of the propanamide group. 4-Fluoroisobutyrylfentanyl is the positional isomer of 4-fluorobutyrfentanyl (4F-BF) and thus both substances are structurally very closely related, which results in the same molecular formula and molecular mass. The molecular structure, molecular formula, and molecular mass of 4-fluoroisobutyrylfentanyl are provided in Figure 1.

The first reference to 4-fluoroisobutyrylfentanyl in the scientific literature appears to have been in a paper published in 1999, wherein the synthesis of the substance and analytical discrimination from fentanyl was reported (Ohta, 1999).

FIGURE 1
The molecular structure, molecular formula and molecular mass of 4-fluoroisobutyrylfentanyl (left), 4-fluorobutyrylfentanyl (middle) and fentanyl (right).

4-fluoroisobutyrylfentanyl	**4-fluorobutyrylfentanyl**	**Fentanyl**
		
$C_{23}H_{29}FN_2O$	$C_{23}H_{29}FN_2O$	$C_{22}H_{28}N_2O$
368.50 g/mol	368.50 g/mol	336.48 g/mol

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-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide

Chemical Abstract name:

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]propanamide

Other names:

N-(4-Fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide;

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]propanamide;

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)-4-piperidyl]propanamide;

N-(4-Fluorophenyl)-*N*-(1-phenethyl-4-piperidinyl)isobutyramide;

N-(4-Fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl) isobutyramide

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

244195-32-2.

PubChem SID:

Could not be identified ([7]).

IUPAC International Chemical Identifier Key (InCHI Key)([8]):

OZDOSQNUJIXEOR-UHFFFAOYSA-N
*SMILES ([9]):*CC(C)C(=O)N(C1CCN(CC1)CCC2=CC=CC=C2)C3=CC=C(F)C=C3

Common names:

4-fluoroisobutyrylfentanyl, 4-fluoro-isobutyrylfentanyl, 4-fluoro-isobutyrfentanyl, para-fluoroisobutyrylfentanyl, 4-F-iBF, 4-FiBF, 4-FIBF, FIBF, p-FIBF, p-FiBF.

Street names:

The street names for 4-fluoroisobutyrylfentanyl may include the common names.

Identification and analytical profile

Physical description

4-Fluoroisobutyrylfentanyl hydrochloride has been described as a neat solid (Cayman Chemical Company, 2017) and as a white powder (base) (SWGDRUG, 2016). 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. 4-Fluoroisobutyrylfentanyl is expected to be lipophilic. This substance has been seized as a powder, in tablet form, and as a liquid. A more detailed description of seizures and collected samples can be found in Section C.

Chemical stability and typical reactions

Specific information about 4-fluoroisobutyrylfentanyl could not be identified. For long-term storage it is recommended that 4-fluoroisobutyrylfentanyl, supplied as a solid, is stored at -20 °C (Cayman Chemical Company, 2017)

Analytical profile

As summarized in Table 1, some analytical data have been published.

It is possible that immunoassays for fentanyl may not distinguish between 4-fluoroisobutyrylfentanyl and fentanyl due to the structural similarity between the two substances. Identification of 4-fluoroisobutyrylfentanyl therefore would require further confirmatory analysis using more suitable

([6]) The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.
([7]) As of 21.10.2017
([8]) InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.
([9]) The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

detection techniques based on, for example, (tandem) mass spectrometry (Helander et al., 2017). Similarly, 4-fluoroisobutyrylfentanyl is not expected to give a positive response to tests developed for morphine-type opioids. An analytical challenge might arise from the number of potential positional isomers that could exist as a result of the presence of the fluorine atom. For example, three fluorophenyl and three fluorophenylethyl isomers (2F-, 3F-, 4F-) can exist when just considering the two phenyl rings present in the molecule. These six isomers could also apply to the 4-fluorobutyrylfentanyl counterparts, thus, potentially giving rise to twelve isomers. Information about the detection of isomers other than 4-fluoroisobutyrylfentanyl could not be identified. The availability of standard reference material is recommended in order to facilitate their differentiation.

Analytical difficulty arises due to the isobaric nature and very similar fragmentation patters of 4-fluoroisobutyrylfentanyl and 4-fluorobutyrylfentanyl. Forensic laboratories, being aware of this, often report results as ‘4-fluoroisobutyrylfentanyl/4-fluorobutyrylfentanyl’ for samples where the isobaric substances were not, or could not be, separated.

TABLE 1
Information associated with the detection and chemical analysis of 4-fluoroisobutyrylfentanyl (amongst other substances). [a]

Techniques [b]	Comment	Reference
TLC, GC-FID, direct inlet EI-MS, IR	Synthesis and analytical characterisation.	Ohta et al. (1999)
^{1}H-NMR, GC-MS, FTIR-ATR	Analytical characterisation of reference material.	SWGDRUG (2016)
GC-MS	Analytical characterisation of reference material.	Cayman Chemical Company (2017)
GC-MS, LC-MS/MS	Blood analysis of 'overdose' cases.	DeRienz et al. (2017)
LC-MS(/MS)	Analysis of serum and urine sample obtained from an intoxication case in September 2016.	Helander et al. (2017)
LC-MS/MS	Method validation and application to analysis of postmortem biological sample material.	Kahl et al. (2017)
GC-MS	Retrospective analysis of GC-MS results obtained from blood samples.	Newmeyer et al. (2017)
GC-MS, GC-NPD	Detection in blood sample.	Poston et al. (2017)
GC-MS, GC-FTIR (condensed phase)	Analytical characterisation of reference material.	Slovenian National Forensic Laboratory (2017)
GC-MS	Analysis of drug paraphernalia (spoon residue) found at the site of fatal intoxication.[c]	Swanson et al. (2017)
LC-MS/MS	Analysis of postmortem and human performance toxicology casework	Turri et al. (2017)
LC-MS(/MS)	In vitro metabolism using pooled human hepatocytes and analysis of authentic human urine samples.	Watanabe et al. (2017)
GC-MS, LC-MS	Analysis of drug paraphernalia (spoon residue) and analysis of postmortem blood specimen.	Zaney et al. (2017)

[a] As of 21 October 2017.
[b] TLC: Thin-layer chromatography; GC: gas chromatography; FID: flame ionization detection; EI: electron ionization; MS: mass spectrometry; IR: infrared spectroscopy; NMR: nuclear magnetic resonance spectroscopy; FT: Fourier transform; ATR: attenuated total reflectance; LC: liquid chromatography; MS/MS: tandem MS; NPD: nitrogen phosphorus detector;
[c] Identification based on mass spectral library comparison only.

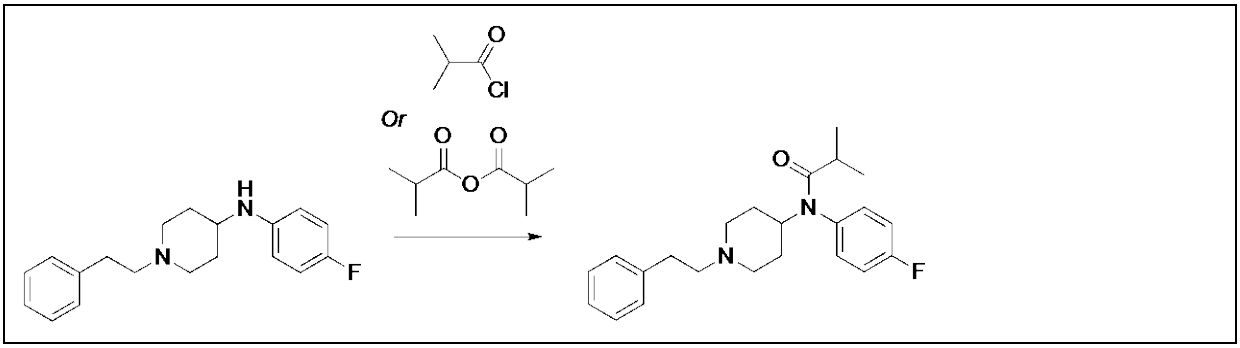
Methods and chemical precursors used for the manufacture

No information was reported by the Member States, Turkey, or Norway, about the chemical precursors or manufacturing methods used to make the 4-fluoroisobutyrylfentanyl that has been detected within Europe.

Synthesis

A synthesis procedure for 4-fluoroisobutyrylfentanyl could not be identified in the published literature but it seems 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 adapted for the multistep synthesis of fentanyl are applicable to 4-fluoroisobutyrylfentanyl whereby the final reaction step is expected to apply the acylation of the *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine intermediate, a precursor analogous to the *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) intermediate involved in the preparation of fentanyl and many of its analogues (Figure 2) ([10]).

FIGURE 2
A possible final step of the synthesis of 4-fluoroisobutyrylfentanyl employing the acylation of the *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine intermediate using either isobutyryl chloride or isobutyric anhydride.



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, 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).

([10]) Methods not relying on the controlled precursor NPP for the synthesis of 4-fluoroisobutyrylfentanyl are possible. For example, alkylation of N-(4-fluorophenyl)-2-methyl-N-(piperidin-4-yl)propanamide by phenethyl chloride would afford the title product.

In contrast to the 4-ANPP and its precursor *N*-phenethyl-4-piperidone (NPP), which 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; INCB, 2017), the fluorinated analogue of 4-ANPP used for the preparation of 4-fluoroisobutyrylfentanyl is not an internationally controlled substance.

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 (Section C). A potentially detectable impurity might be predicted to include the *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine intermediate .

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA have noted that 4-fluoroisobutyrylfentanyl has typically been detected in powders, tablets and liquids (Section C).

A1.3. Route of administration and dosage

As with other fentanils, 4-fluoroisobutyrylfentanyl 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). There are also instances where 4-fluoroisobutyrylfentanyl is advertised for sale in the form of blotters by Internet vendors. Users have also described rectal administrations ([11]).

Of note is the apparent popularity of selling ready-to-use or homemade nasal sprays containing solutions for the administration of fentanils. It is worth noting that some of these products are not always labelled and/or sold as another substance, a phenomenon that extends to the use of other fentanils that have appeared in Europe in the past few years, including acryloylfentanyl (EMCDDA 2017b; EMCDDA 2017d; Ujváry et al., 2017) and furanylfentanyl (EMCDDA, 2017c; EMCDDA, 2017e).

Dosage

Limited information is available regarding the dose and the dose regimens of 4-fluoroisobutyrylfentanyl. Reports available on user discussion forums included single intravenous administrations up to 5 mg followed by nasal spray administrations reportedly amounting to 3 mg over a six-hour period ([12]). Other examples included nasal administrations of 5 mg per day ([13]); “dosing every 2-3 hours (0.7 mg/mL)… up to about 0.35 mg IV” ([11]); 0.1–0.5 ml intravenous injections of 0.69 mg/mL solutions and 2 mL rectal administrations using the same concentration ([11]); self-prepared nasal spray concentrations of 10–15 mg/mL have also been mentioned ([14]).

From this, however, it is not possible to 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.

([11]) http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrfentanyl-(4-FiBF-p-FiBF)/page2 (last accessed: 22.10.2017).
([12]) https://erowid.org/experiences/exp_pdf.php?ID=106906&format=pdf (last accessed 21.10.2017).
([13]) http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrfentanyl-(4-FiBF-p-FiBF) (last accessed 21.10.2017).
([14]) https://www.reddit.com/r/opiates/comments/3ved25/anybody_try_furanylfentanyl_fuf_or/ (last accessed 21.10.2017).

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacologically, 4-fluoroisobutyrylfentanyl is an opioid receptor agonist.

Pharmacodynamics

In vitro studies

The currently available data suggests that 4-fluoroisobutyrylfentanyl binds to the μ-opioid receptor (MOR) with high selectivity over the κ- and δ-opioid receptors (KOR and DOR) (Table 2) ([15]) (US DEA, 2017b).

Table 2 provides a summary of binding and functional activity data that illustrate that 4-fluoroisobutyrylfentanyl (EC_{50} = 115 nM, [^{35}S]GTPγS binding assay, E_{max} = 91.6%) functioned as a MOR agonist ([16]). In comparison, morphine (EC_{50} = 17.2 nM, [^{35}S]GTPγS binding assay, E_{max} = 86.1%) and fentanyl (EC_{50} = 28.8 nM, E_{max} = 94.0%) were several times more potent than 4-fluoroisobutyrylfentanyl and all three test drugs exhibited comparable efficacy (E_{max}) using this particular in vitro assay.

4-Fluoroisobutyrylfentanyl showed relatively low affinity toward KOR (K_i = 2,700 nM) with moderate to low potency and moderate relative efficacy (EC_{50} = 1,330 nM, [^{35}S]GTPγS binding assay, E_{max} = 49.3%). As far as DOR was concerned, binding affinity and potency were relatively low, whereas efficacy was moderate (K_i = 1,670 nM, EC_{50} = 2,490 nM, [^{35}S]GTPγS binding assay, E_{max} = 64%), which suggested a MOR selective profile, at least under these *in vitro* conditions. All test drugs used as positive control were shown to be efficacious agonists (Table 2).

TABLE 2
Binding and functional activity data for 4-fluoroisobutyrylfentanyl (4F-iBF) generated via the Drug Enforcement Administration–Veterans Affairs (DEA-VA) Interagency Agreement (modified from US DEA, 2017b).

MOR	4F-iBF [b]	DAMGO	Morphine	Fentanyl	Naltrexone
[^{3}H]DAMGO binding Ki (nM)	0.451 ± 0.046	0.277 ± 0.027	0.322 ± 0.048	0.144 ± 0.024	0.082 ± 0.011
IC_{50} (nM)	2.16 ± 0.20	–	–	–	–
[^{35}S]GTPγS binding	**4F-iBF [b]**	**DAMGO**	**Morphine**	**Fentanyl**	
Stimulation EC_{50} (nM)	115 ± 33	22.4 ± 7.0	17.2 ± 4.5	28.8 ± 6.9	–
Maximal stimulation (%)*	91.6 ± 4.1	96.1 ± 2.2	86.1 ± 5.0	94.0 ± 6.0	–
DOR	**4F-iBF [b]**	**DPDPE-OH**	**Morphine**	**Fentanyl**	**Naltrexone**
[^{3}H]DPDPE binding K_i (nM)	1,670 ± 410	1.93 ± 0.14	79.1 ± 5.1	164 ± 13	8.7 ± 1.0

([15]) K_i represents the equilibrium inhibition constant for the test drug displacing the radioligand.
([16]) EC_{50} represents the concentration that causes a half-maximal response of the agonist.

IC_{50} (nM)	2,790 ± 630	–	–	–	–
[^{35}S]GTPγS binding	**4F-iBF** [b]	**DPDPE-OH**	**Morphine**	**Fentanyl**	
Stimulation EC_{50} (nM)	2,490 ± 390	7.4 ± 1.6	750 ± 160	996 ± 99	–
Maximal stimulation (%)*	64 ± 15	98.90 ± 0.76	64.0 ± 9.7	42.5 ± 3.6	–
KOR	**4F-iBF** [b]	**U-50,488H**	**Morphine**	**Fentanyl**	**Nor-BNI**
[^{3}H]U-69,593 binding K_i (nM)	2,700 ± 490	0.143 ± 0.043	34.9 ± 7.0	224 ± 36	0.53 ± 0.17
IC_{50} (nM)	4,830 ± 790	–	–	–	–
[^{35}S]GTPγS binding	**4F-iBF** [b]	**U-50,488H**	**Morphine**	**Fentanyl**	–
Stimulation EC_{50} (nM)	1,330 ± 290	1.89 ± 0.30	81 ± 10	347 ± 65	–
Maximal stimulation (%)*	49.3 ± 5.8	98.1 ± 1.2	87.3 ± 6.7	74.9 ± 9.0	–

[a] 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), U-50,488H (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.

[b] 4F-iBF: 4-fluoroisobutyrylfentanyl.

Animal studies

It has recently been reported that 4-fluoroisobutyryfentanyl showed analgesic effects in mice (subcutaneous administration) in the tail-flick test (55°C). The ED_{50} value for 4-fluoroisobutyryfentanyl was determined at 1.61 mg/kg, compared to 0.122 mg/kg for fentanyl, and 12 mg/kg for morphine. It was furthermore reported that naltrexone administration (10 mg/kg, s.c.) affected nociceptive effects as demonstrated by a corresponding shift of the dose-response curve to the right (WHO, 2017) ([17]).

Pharmacokinetics

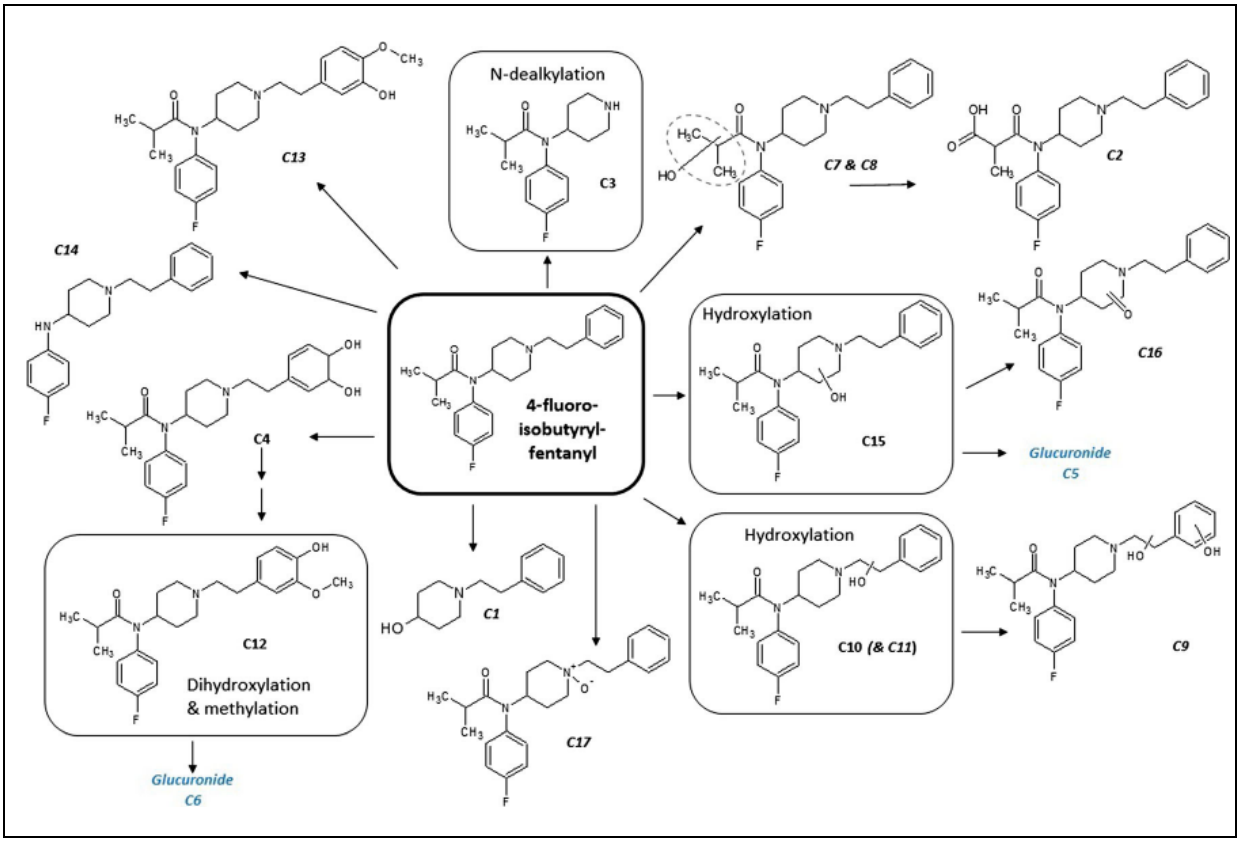
A recent *in vitro* investigation using human hepatocytes (10 µM test drug, up to 5 h incubation time) identified 17 metabolites (Figure 3). The identified biotransformations included *N*-dealkylation (C3), hydroxylation (C7, C8, C10, C11, C15, C17) followed by glucuronidation (C5), dihydroxylation (C9), dihydrodiol formation (C4), dihydroxylation with methylation (C12, C13) followed by glucuronidation (C6), amide hydrolysis (C14), oxidative *N*-dealkylation, and further reduction of the keto group (C1), carboxylation (C2), and carbonylation (C16) (Figure 3) (Watanabe et al., 2017).

The parent drug was prevalent in both the hepatocyte incubate and authentic human urine samples. Nine metabolites were observed in hepatocytes (C3, C8, C10, C12, C14–C17) with the desphenethyl ("nor") metabolite C3 ([18]) being the major metabolite in the 5 h sample followed by the monohydroxylated metabolites C15 and C10. Eleven metabolites were detected in hydrolysed urine (C1, C2, C3, C4, C7, C9–C13, C15), which suggested that major metabolites were comparable. The C12 metabolite, a potential target for confirming consumption of 4-fluoroisobutyrylfentanyl, was also identified (Watanabe et al., 2017).

([17]) Data provided by the US Drug Enforcement Administration, Food and Drug Administration, National Center for Toxicological Research (2017b). Report: 4-Fluoroisobutyryl fentanyl (FIBF), Evaluation of analgesic effects using the warm water tail withdrawal assay. 28 June 2017.
([18]) Systematic name: *N*-(4-Fluorophenyl)-2-methyl-*N*-(piperidin-4-yl)propanamide.

FIGURE 3

Proposed metabolic pathway of 4-fluoroisobutyrylfentanyl suggested by Watanabe et al. (2017), which summarize the results obtained from *in vitro* incubations with 10-donor pooled human hepatocytes and authentic human urine samples. Enclosed metabolites: major metabolites detected in hydrolysed human urine specimen; metabolites in italics only found in either the *in vitro* or *in vivo* experiment.



A limited number of self-reported user experiences have noted that the duration of effects induced by 4-fluoroisobutyrylfentanyl could be greater than 12 hours ([19,20]). If correct, then this would indicate a longer lasting activity compared to fentanyl and other fentanyl analogues available on the market. As noted in the introduction, given the difficulties of collecting such data, these reports should be viewed with caution.

Inter-individual genetic variability in metabolising enzymes

For fentanyl, oxidative dealkylation by hepatic CYP3A4 and by CYP3A5 isoenzymes to norfentanyl has been demonstrated (Guitton et al., 1997, Jin et al., 2005, Labroo et al., 1997). The variation of the expression of the genes coding for these CYP3A isoenzymes among populations might be of clinical significance (Meyer and Maurer, 2011) but further studies are needed to address the toxicological consequences of such polymorphisms.

([19]) https://forum.drugs-and-users.org/index.php?topic=3373.0 (last accessed 22.10.2017).
([20]) http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrfentanyl-(4-FiBF-p-FiBF) (last accessed 22.10.2017).

Interactions with other substances and other interactions

Specific information about 4-fluoroisobutyrylfentanyl could not be identified although it seems conceivable that interactions observed with fentanyl might equally apply (Preston, 2016). For example, should 4-fluoroisobutyrylfentanyl 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) ([21]) may result in increased plasma concentration of 4-fluoroisobutyrylfentanyl. This could increase the risk of poisoning, including potentially fatal respiratory depression.

The concomitant use of other central nervous system (CNS) depressants, including other opioids, sedatives/hypnotics (such as the benzodiazepines and the z-drugs), ethanol, 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 4-fluoroisobutyrylfentanyl.

Effects on ability to drive and operate machines

No studies of the effects of 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl.

A3. Psychological and behavioural effects

Information on the psychological and behavioural effects of 4-fluoroisobutyrylfentanyl is limited. It appears that the psychoactive profile of 4-fluoroisobutyrylfentanyl might share at least some similarities with other opioid analgesics such as fentanyl and heroin. These would include relaxation and euphoria; at higher doses, sedation and profound intoxication may occur.

A limited number of self-reported user experiences have noted that 4-fluoroisobutyrylfentanyl is ‘long lasting’ and is less euphorigenic when compared to other opioids ([22,23,24]). As noted in the introduction, given the difficulties of collecting such data, these reports should be viewed with caution. In addition, it should be noted that if 4-fluoroisobutyrylfentanyl was indeed less euphorigenic, this might lead to users increasing the dose, which could increase the risk of opioid toxicity and particularly life-threatening respiratory depression.

([21]) 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
([22]) https://forum.drugs-and-users.org/index.php?topic=3373.0 (last accessed 22.10.2017).
([23]) http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrfentanyl-(4-FiBF-p-FiBF) (last accessed 22.10.2017).
([24]) https://www.reddit.com/r/opiates/comments/3ved25/anybody_try_furanylfentanyl_fuf_or/ (last accessed 22.10.2017).

A4. Legitimate uses of the product

4-Fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl is used for other legitimate purposes.

There are no reported uses of 4-fluoroisobutyrylfentanyl as a component in industrial, cosmetic or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database hosted by the European Chemicals Agency (ECHA) using the CAS Registry Number returned no results.

There is no marketing authorisation (existing, on-going or suspended) for 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl in animal models.

The related des-fluoro analogue, isobutyrylfentanyl (NIH 10487) (Aceto et al., 1988) was studied in rhesus monkeys that received 3.0 mg/kg s.c. of morphine sulfate every 6 h for at least 90 days. In the single dose substitution test in rhesus monkeys, NIH 10487 (evaluated at 0.025 mg/kg and 0.1 mg/kg) “substituted completely for morphine. Potency estimate is 30 times [that of] morphine. Rapid onset and 2.5h duration of action were observed. Sagging, ataxia, slowing and scratching were noted at the highest dose during the first hour”.

B2. Human data

No studies were identified that have investigated the dependence and/or abuse potential of 4-fluoroisobutyrylfentanyl in humans.

Whereas no specific data exist for 4-fluoroisobutyrylfentanyl, 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 4-fluoroisobutyrylfentanyl.

Section C. Prevalence of use

Information from seizures, collected and biological samples

4-Fluoroisobutyrylfentanyl was formally notified on 26 August 2016 by the EMCDDA on behalf of the Slovenia, in accordance with Article 4 of the Council Decision. The Reporting Form details a collected sample of 5 grams of white powder that was test-purchased as part of the EU co-funded RESPONSE project, and analysed on 25 May 2016 in Ljubljana. 4-Fluoroisobutyrylfentanyl was analytically confirmed by GC-MS, HPLC-TOF, FTIR-ATR, GC-MS-IR, ion chromatography and NMR by the Slovenian National Forensic Laboratory and the Faculty of Chemistry and Chemical technology of the University of Ljubljana (EMCDDA, 2017a).

Since then, a total of 5 Member States (Belgium, Germany, Slovenia, Sweden and the United Kingdom) have reported detections ([25]) of 4-fluoroisobutyrylfentanyl (EMCDDA, 2017a).

It is important to note that detections of 4-fluoroisobutyrylfentanyl may be under-reported since the substance is not routinely screened for. Three Member States (Austria, Slovenia and Sweden) and Norway reported that 4-fluoroisobutyrylfentanyl is part of routine screening in some (but not all) laboratories.

Information from seizures

Information reported to the EMCDDA and Europol indicates that 24 seizures of 4-fluoroisobutyrylfentanyl have been reported by 4 Member States: Sweden (20 seizures), Belgium (1), Germany (1), and the United Kingdom (2). The majority of the seizures took place in 2016, while the most recent events took place in 2017.

Additionally, Finland reported a seizure of 0.05 g of a powder which was reported as '2F-, 3F- or 4F-BF; 2F-, 3F- or 4F-iBF', as the exact isomer was not be determined. This case is not discussed further in this report.

No information regarding the purity of the samples was provided.

Powders

A total of 9 seizures of powders were reported by: Belgium, Germany, Sweden, and the United Kingdom, amounting to a total of 378.6 g.

The powder seizure reported by Germany also contained furanylfentanyl. In one case reported by the United Kingdom, the powder also contained furanylfentanyl and an unspecified isomer of 'fluorofentanyl'.

In the other seizure reported by the United Kingdom, a number of different items were seized, and different substances identified, including heroin, cocaine, steroids and synthetic cannabinoids (5F-MDMB-PINACA and MMB-FUBINACA). Nine of the items were found to contain 4-fluoroisobutyrylfentanyl, as follows:

- 0.436 grams of crystalline powder which appeared to be pure 4-fluoroisobutyrylfentanyl (no other compounds detected in the crystals);

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

- 0.425 grams of brown powder, found to contain mainly 4-fluoroisobutyrylfentanyl mixed with smaller amounts of paracetamol and caffeine;
- 7 items, consisting of heroin containing paracetamol, caffeine and 4-fluoroisobutyrylfentanyl. These were of various strengths of heroin and 4-fluoroisobutyrylfentanyl which were not determined. The total weight of these powders was 105.8 g.

Other physical forms

Sweden reported seizures of 4-fluoroisobutyrylfentanyl in tablets and liquids, as follows:

- 12 seizures of tablets, amounting to a total of 6727 tablets;
- 3 seizures of liquids, amounting to a total of 208 millilitres.

Information from collected samples

Slovenia reported a sample of 5 g of 4-fluoroisobutyrylfentanyl base in powder form which was purchased from an Internet vendor. The sample was apparently shipped from China and was received in May 2016. No other substances were detected in the sample.

Information from biological samples

Serious adverse events (deaths and acute intoxications) with confirmed exposure to 4-fluoroisobutyrylfentanyl from biological samples are discussed in Section D.

Availability, supply, price

Information on production

No information was received in relation to the production of 4-fluoroisobutyrylfentanyl.

Information on trafficking

No information was reported to the EMCDDA in relation to the trafficking of 4-fluoroisobutyrylfentanyl. Information on the source of 4-fluoroisobutyrylfentanyl is limited to one report regarding collected sample of the substance. Here, the substance was ordered from an online vendor apparently based in China (see above). In addition, Belgium reported a seizure of 4-fluoroisobutyrylfentanyl to the EMCCDA where the final destination was Germany.

Availability from Internet vendors

A structured search of online vendors on the surface web by the EMCDDA ([26]) found that the substance is offered for sale online in small and wholesale amounts, typically as a ‘research chemical’ and as powders, liquids, and blotters.

On the websites identified, 4-fluoroisobutyrylfentanyl was available in powder, liquid and blotter form. For powders, amounts on sale ranged from 0.5 grams to 10 kg, for liquids 5 to 50 mL and for blotters 1 to 500 units. Prices varied according to the amounts on sale. Powders ranged from EUR 0.7 per gram to EUR 238 per gram. Liquids and blotters were only sold in one internet retailer. The price of the liquids varied from EUR 1 to EUR 5 per mL; for blotters a price of EUR 1 per unit was indicated.

The availability of 4-fluoroisobutyrylfentanyl on the darknet is not currently known.

([26]) The search for online vendors of 4-fluoroisobutyrylfentanyl on the surface web was performed on 06/06/2017 using previously established methodology (EMCDDA, 2017c). The search identified 31 vendors that appeared to be based in, and/or claim to have presence in China (n=18), India (n=3), USA (n=2), Hong Kong (n=2), Hungary (n=1), Sweden (n=1), Turkey (n=1) and European Union (not specified) (n=1); the remaining 2 websites did not list a location. Nineteen websites listed quantities and prices for4-fluoroisobutyrylfentanyl. The remaining websites only provided prices on request.

Prevalence of use

No studies were identified that have investigated the prevalence of use of 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

Data on the acute toxicity, abuse liability, and dependence producing potential of 4-fluoroisobutyrylfentanyl could not be identified.

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of 4-fluoroisobutyrylfentanyl and/or its metabolites in humans. Although the pharmacology and toxicology of 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl (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).

There is a lack of information on the clinical features of poisoning caused by 4-fluoroisobutyrylfentanyl. Nonetheless, the available data suggests that the nature of the effects of 4-fluoroisobutyrylfentanyl share some similarities with opioid analgesics such as morphine and fentanyl. As a result, features of poisoning are likely to include reduced level of consciousness or unconsciousness, respiratory depression and arrest, and miosis ([27]).

Acute intoxications reported by the Member States

No acute intoxications with confirmed exposure to 4-fluoroisobutyrylfentanyl were reported ([27,28]).

Acute intoxications identified from other sources

No cases of acute intoxications were identified from other sources ([27]).

Deaths reported by the Member States

A total of 20 deaths were reported by 2 Member States: Sweden (16) and the United Kingdom (4). Exposure to 4-fluoroisobutyrylfentanyl was analytically confirmed in post-mortem samples in all cases from Sweden; no reference standard was available to distinguish between 4-fluoroisobutyrylfentanyl and 4-fluorobutyrylfentanyl in cases from the United Kingdom.

The deaths occurred between July 2016 and March 2017, with 17 occurring in 2016 and 3 in 2017.

Of the 18 deaths where demographic data were available, 16 were male (80%) and 2 were female (20%). The mean age of the males was 35 years (median 34) and ranged from 20 to 52 years; the age of the females was 24 and 36 years.

Circumstances and cause of death

In the majority of cases there was a lack of information regarding any symptoms experienced by the deceased prior to death, but, where described in a few cases, the deceased had become unconscious and in one case the deceased was found convulsing. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's). Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

The cause of death was reported in 16 out of 20 cases. In at least 13 deaths, intoxication with 4-fluoroisobutyrylfentanyl 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 19 cases (with creatinine detected in the remaining case).

([27]) Information on the clinical features of intoxication caused by 4-fluoroisobutyrylfentanyl is limited to a single report involving a death published by Helander et al., (2017). In this case, a male user had apparently injected intravenously 250 mg of 4-fluoroisobutyrylfentanyl and was 'discovered lifeless'. The main features reported were unconsciousness, apnoea, and asystole. The patient 'was discovered lifeless with a syringe reportedly containing "4-iBF" next to him. Cardiopulmonary resuscitation (CPR) was initiated by relatives. On ambulance arrival, the first recorded rhythm was asystole and CPR was maintained with an automated device. He was given 0.4mg of naloxone and repeated 1mg doses of adrenaline intravenously. Palpable pulses appeared only transiently and CPR was maintained during transport to hospital. Return of spontaneous circulation occurred after 90 min of CPR. The patient was unconscious (RLS 8), had dilated pupils unresponsive to light, and was normothermic. He was intubated, put on ventilator, and mildly therapeutically cooled to the target 36 (C (96.8 (F) body temperature, according to hospital guidelines. An early computed tomography (CT) showed brain edema. His neurological condition did not improve during the following 24 h and he was declared dead 43 h after arriving to hospital' (Helander et al., 2017). This case is included in the deaths reported by the Member States.

([28]) Sweden reported 2 acute intoxications with suspected exposure to 4-fluoroisobutyrylfentanyl. These cases are not discussed further in this report.

4-Fluoroisobutyrylfentanyl was quantified in 16 cases. Post-mortem femoral blood concentrations ranged from 0.76 to 370 ng/g blood (median 41 ng/g blood). In 2 cases, although the concentration was measured (44 and 85 ng/mL), it was not possible to determine if it related to 4-fluoroisobutyrylfentanyl or 4-fluorobutyrylfentanyl. Due to the toxicity of potent opioids and variability in user tolerance, determination of a 'fatal' concentration based on a post-mortem blood concentration is not 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 deaths, including: cannabinoids, benzodiazepines, amphetamine, zopiclone, zolpidem, gabapentinoids (pregabalin and gabapentin), antidepressants, antipsychotics, antihistamines, a synthetic cathinone (alpha-PHP), ketamine and ethanol. Other opiates/opioids were detected in 9 of the deaths; codeine, buprenorphine, tramadol, methadone, oxycodone, fentanyl, despropionylfentanyl, tetrahydrofuranylfentanyl, and acryloylfentanyl.

Overall, whilst other substances may have contributed some toxicity, a synergistic effect with 4-fluoroisobutyrylfentanyl would have been likely with other central nervous system depressants such as ethanol, benzodiazepines, opioids, etc. Nevertheless, the potent opioid nature of 4-fluoroisobutyrylfentanyl means that the primary toxic contribution could be attributed to 4-fluoroisobutyrylfentanyl and death may not have occurred if 4-fluoroisobutyrylfentanyl had not been used. An assessment of the Toxicological Significance Score (TSS) (Elliott, Sedefov, & Evans-Brown, 2017) incorporating the above considerations shows that 4-fluoroisobutyrylfentanyl had a TSS value of 3 (high) in 15 out of 16 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 cause of death (drowning) was cited (TSS value of 1, low). The 4 cases where 4-fluoroisobutyrylfentanyl could not be unequivocally confirmed were not part of the assessment.

Deaths identified from other sources

Since August 2016, more than 60 deaths associated with 4-fluoroisobutyrylfentanyl have been reported in the United States (US DEA, 2017b).

D2. Chronic health effects

D2.1. Animal data

No studies were identified that have investigated the chronic health effects of 4-fluoroisobutyrylfentanyl in animals.

D2.2. Human data

No studies were identified that have investigated the chronic health effects of 4-fluoroisobutyrylfentanyl in humans.

D3. Factors affecting public health risks

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

4-Fluoroisobutyrylfentanyl is being sold on the surface web as a drug in its own right. It is sold in both retail and wholesale quantities. It has been sold as a 'research chemical' in powder form, liquids, and blotters.

4-Fluoroisobutyrylfentanyl is also used to make tablets, as evidenced by the 12 seizures by Swedish Police of 6727 tablets. No further details are available on these cases.

Information from a seizure case in the United Kingdom suggests that 4-fluoroisobutyrylfentanyl has been sold on the illicit opioid market in mixtures with heroin.

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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl. Section C (above) and Section E6 (below) provides additional information on the likely user groups of 4-fluoroisobutyrylfentanyl.

D3.4. Nature and extent of health consequences

Acute health risks

Although the pharmacology and toxicology of 4-fluoroisobutyrylfentanyl 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; Romberg et al., 2003).

Similar to other opioid analgesics, the most serious acute risk arising from the use of 4-fluoroisobutyrylfentanyl 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);
- 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);
- 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, 2016b; 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 (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 4-fluoroisobutyrylfentanyl (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 carfentanil 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 4-fluoroisobutyrylfentanyl 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 under which 4-fluoroisobutyrylfentanyl is obtained and used. 4-Fluoroisobutyrylfentanyl is offered for sale on the surface web as a powder, liquids, and blotters.

It has also been seized as tablets. Information from a seizure case in the United Kingdom suggests that 4-fluoroisobutyrylfentanyl has been sold on the illicit opioid market in mixtures with heroin.

Section E. Social risks

While there have been no studies on the social risks of 4-fluoroisobutyrylfentanyl, 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 4-fluoroisobutyrylfentanyl. Given that 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl on the direct social environment. Given that 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl.

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

There are no data on the possible effects of 4-fluoroisobutyrylfentanyl 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 4-fluoroisobutyrylfentanyl to specific user groups (aside from psychonauts), it is reasonable to assume 4-fluoroisobutyrylfentanyl 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 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 4-fluoroisobutyrylfentanyl.

Slovenia reported a collected sample of 4-fluoroisobutyrylfentanyl to both Europol and the EMCDDA where the country of origin was indicated as China.

Belgium reported a seizure of 4-fluoroisobutyrylfentanyl to the EMCCDA where the final destination was Germany.

The seizure of an illicit laboratory producing fentanils in Europe in 2013 (EMCDDA, 2017e) 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 4-fluoroisobutyrylfentanyl on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances.

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

No information was reported nor identified concerning evidence of the same groups of people being involved in different types of crime related to the availability of 4-fluoroisobutyrylfentanyl.

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 4-fluoroisobutyrylfentanyl.

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 4-fluoroisobutyrylfentanyl.

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 4-fluoroisobutyrylfentanyl.

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 4-fluoroisobutyrylfentanyl.

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 4-fluoroisobutyrylfentanyl.

References

Aceto, M., Bowman, E., Harris, L. and May, E. (1988), 'Dependence studies of new compounds in the rhesus monkey, rat, and mouse, 1987', in L. S. Harris (ed.), *Problems of Drug Dependence, 1987*, NIDA Research Monograph Series 81, pp. 485–542, U.S. Department of Health and Human Services, Rockville, Maryland.

Cayman Chemical Company (2017), 'FIBF (hydrochloride) product information'. 14 April 2017. Cayman Chemical Company, Ann Arbor, M, USA. Available at: https://www.caymanchem.com/pdfs/19313.pdf.

Cole, J. B., & Nelson, L. S. (2017), 'Controversies and carfentanil: We have much to learn about the present state of opioid poisoning'. *The American Journal of Emergency Medicine*. https://doi.org/10.1016/j.ajem.2017.08.045

Commission on Narcotic Drugs (CND) (2017), *The International Drug Control Conventions. Tables of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, as at 18 October 2017*. https://documents-dds-ny.un.org/doc/UNDOC/GEN/V17/033/35/PDF/V1703335.pdf?OpenElement

Council of the European Union (CUE) (2017), *Council implementing decision (EU) 2017/1774 of 25 September 2017 on subjecting N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide (acryloylfentanyl) to control measures*, Official Journal of the European Union, L 251/21. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017D1774

Cox, B. M. (2011), 'Pharmacology of opioid drugs', in: *G. Pasternak (ed) The opiate receptors*. Springer, pp. 23–58.

Dahan, A., Sarton, E., Teppema, L., Olievier, C., Nieuwenhuijs, D., Matthes, H. W. and Kieffer B. L. (2001), 'Anesthetic potency and influence of morphine and sevoflurane on respiration in mu-opioid receptor knockout mice', *Anesthesiology*, 2001, 94(5), pp. 824–832. http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1944782

de Boer, D., Goemans W. P. J., Ghezavat, V. R., van Ooijen, R. D., Maes, R. A. (2003), 'Seizure of illicitly produced para-fluorofentanyl: quantitative analysis of the content of capsules and tablets', *Journal of Pharmaceutical and Biomedical Analysis*, 31(3), pp. 557–562.

DeRienz, R. T., Baker, D. D., Hogue, J., et al. (2017), 'An efficient screening approach for fentanyl analogs using a single extraction sequential GC/MS and LC/MS/MS analysis' (Abstract). 2017 SOFT-TIAFT Meeting, Boca Raton, FL, September 9–14, 2017. Programme book, p. 108.

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

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2015), *Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone*, EMCDDA Papers, Publications Office of the European Union, Luxembourg. http://www.emcdda.europa.eu/system/files/publications/932/TDAU14009ENN.web_.pdf

EMCDDA (2016a), *EMCDDA-Europol Joint Report on a new psychoactive substance:* N-*phenyl*-N-*[1-(2-phenylethyl)piperidin-4-yl]acetamide (acetylfentanyl)*. In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, Publications Office of the European Union, Luxembourg. https://doi.org/10.2810/890694

EMCDDA (2016b), *Preventing opioid overdose deaths with take-home naloxone*, EMCDDA Insights, Publications Office of the European Union, Luxembourg. https://doi.org/10.2810/357062

EMCDDA (2017a), *EMCDDA-Europol Joint Report on a new psychoactive substance: N-(4-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)isobutyramide (4-fluoroisobutyrylfentanyl; 4F-iBF)*. In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, Publications Office of the European Union, Luxembourg. https://doi.org/10.2810/033972

EMCDDA (2017b), *EMCDDA-Europol Joint Report on a new psychoactive substance: N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide (acryloylfentanyl).* In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, Publications Office of the European Union, Luxembourg. https://doi.org/10.2810/87713

EMCDDA (2017c), *EMCDDA-Europol Joint Report on a new psychoactive substance: N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]-furan-2-carboxamide (furanylfentanyl)*. In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, Publications Office of the European Union, Luxembourg. https://doi.org/10.2810/83192

EMCDDA (2017d), *Report on the risk assessment of N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide (acryloylfentanyl) in the framework of the Council Decision on new psychoactive substances*, Publications Office of the European Union, Luxembourg.

EMCDDA (2017e), *Report on the risk assessment of N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) in the framework of the Council Decision on new psychoactive substances*, Publications Office of the European Union, Luxembourg.

Guitton, J., Désage, M., Alamercery, S., et al. (1997), 'Gas chromatographic-mass spectrometry and gas chromatographic-Fourier transform infrared spectroscopy assay for the simultaneous identification of fentanyl metabolites', *Journal of Chromatography B*, 693(1), pp. 59–70.

Helander, A., Bäckberg, M., Signell, P., et al. (2017), 'Intoxications involving acrylfentanyl and other novel designer fentanyls - results from the Swedish STRIDA project', *Clinical Toxicology*, 55(6), pp. 589–599.

InterAgency Board for Equipment Standardization and Interoperability (IAB) (2017), *Recommendations on selection and use of personal protective equipment and decontamination products for first responders against exposure hazards to synthetic opioids, including fentanyl and fentanyl analogues*. https://www.interagencyboard.org/sites/default/files/publications/IAB%20First%20Responder%20PPE%20and%20Decontamination%20Recommendations%20for%20Fentanyl.pdf

International Narcotics Control Board (INCB) (2017), *INCB: Scheduling of fentanyl precursors comes into force*. 18 October 2017. https://www.incb.org/incb/en/news/press-releases/2017/press_release_20171018.html

Jin, M., Gock, S. B., Jannetto, P. J., et al. (2005), 'Pharmacogenomics as molecular autopsy for forensic toxicology: genotyping cytochrome P450 *3A4*1B* and *3A5*3* for 25 fentanyl cases', *Journal of Analytical Toxicology*, 29(7), pp. 590–598.

Kahl, J. H., Gonyea, J., Humphrey, S. M., et al. (2017), 'Validation of a comprehensive UHPLC-MS/MS method to quantify six novel fentanyl analogues in postmortem specimens' (Abstract). 2017 SOFT-TIAFT Meeting, Boca Raton, FL, September 9–14, 2017. Programme book, p. 109.

Keegan, F., Bell, R. G., Crystal, R, and Weiss, M. B. (2017), Nasal drug products and methods of their use. US Patent application 2017/0071851 (Mar. 15, 2017) by Adapt Pharma Ltd. and Opiant Pharmaceuticals.

Kim, H. K. and Nelson, L.S. (2015), 'Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review', *Expert Opinion on Drug Safety*, 14(7), pp. 1137–1146. https://doi.org/10.1517/14740338.2015.1037274

Klar, S. A., Brodkin, E., Gibson, E., Padhi, S., Predy, C., Green, C. and Lee, V. (2016), 'Furanyl-fentanyl overdose events caused by smoking contaminated crack cocaine—British Columbia, Canada, July 15–18, 2016', *MMWR. Morbidity and Mortality Weekly Report*, 65(37), pp. 1015–1016.

Labroo, R. B., Paine, M. F., Thummel, K. E., et al. (1997), 'Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: Implications for interindividual variability in disposition, efficacy, and drug interactions', *Drug Metabolism and Disposition*, 25(9), pp. 1072–1080.

Lynch, M. J., Suyama, J., & Guyette, F. X. (2017), 'Scene safety and force protection in the era of ultra-potent opioids', *Prehospital Emergency Care*, pp. 1–6. https://doi.org/10.1080/10903127.2017.1367446

Macleod, D. B., Habib, A. S., Ikeda, K., Spyker, D. A., Cassella, J. V., Ho, K. Y., Gan, T. J. (2012), 'Inhaled fentanyl aerosol in healthy volunteers: pharmacokinetics and pharmacodynamics', *Anesthesia and Analgesia*, 115(5), pp. 1071-1077. https://doi.org/10.1213/ANE.0b013e3182691898

Meyer, M. R. and Maurer, H. H. (2011), 'Absorption, distribution, metabolism and excretion pharmacogenomics of drugs of abuse', *Pharmacogenomics*, 12(2), pp. 215–233.

Moffat, A. C., Osselton, M. D., Widdop, B., et al. (eds) (2016). 'Clarke's Analysis of Drugs and Poisons', *Pharmaceutical Press, London, Fentanyl Monograph*. https://www.medicinescomplete.com/mc/clarke/current/c-d1e495336.htm?q=fentanyl&t=search&ss=text&tot=63&p=1 - _hit.

Moss, M. J., Warrick, B. J., Nelson, L. S., McKay, C. A., Dubé, P-A., Gosselin, S., Palmer, R. B. and Stolbach, A. I. (2017), 'ACMT and AACT position statement: preventing occupational fentanyl and fentanyl analog exposure to emergency responders', *Clinical Toxicology (Philadelphia)*. https://doi.org/10.1007/s13181-017-0628-2

Newmeyer, M. N., Mazari, P. M., Jufer-Phipps, R. A., et al. (2017), 'Postmortem detection of despropionyl fentanyl in drug related deaths' (Abstract). 2017 SOFT-TIAFT Meeting, Boca Raton, FL, September 9–14, 2017. Programme book, p. 106.

Ohta, H., Suzuki, S. and Ogasawara, K. (1999), 'Studies on fentanyl and related compounds IV. Chromatographic and spectrometric discrimination of fentanyl and its derivatives', *Journal of Analytical Toxicology*, 23(4), pp. 280–285.

Pattinson, K. T. S. (2008), 'Opioids and the control of respiration', *British Journal of Anaesthesia*, 100(6), pp. 747–758.

Poston, A., Jufer-Phipps, R. A., Levine, B. S., et al. (2017), 'Postmortem distribution of *N*-ethylpentylone' (Abstract). 2017 SOFT-TIAFT Meeting, Boca Raton, FL, September 9–14, 2017. Programme book, p. 460–461.

Preston, C. L. (ed) (2016), '*Stockley's Drug Interactions'. Pharmaceutical Press, London. Interactions of Fentanyl.* https://www.medicinescomplete.com/mc/stockley/current/int-cAACD134.htm?q=fentanyl&t=search&ss=text&tot=74&p=1 - _hit

Romberg, R., Sarton, E., Teppema, L., et al. (2003), 'Comparison of morphine-6-glucuronide and morphine on respiratory depressant and antinociceptive responses in wild type and mu-opioid receptor deficient mice', *British Journal of Anaesthesia*, 91(6), pp. 862–870.

San Francisco Department of Public Health (SFDPH) (2015), Severe opioid overdoses in San Francisco caused by fentanyl-containing "Xanax" pill. 10-22-2015. http://www.sfcdcp.org/document.html?id=1005

Somerville, N. J., O'Donnell, J., Gladden, R. M., Zibbell, J. E., Green, T. C., Younkin, M., Ruiz, S., Babakhanlou-Chase, H., Chan, M., Callis, B. P., Kuramoto-Crawford, J., Nields, H. M., Walley, A. Y., (2017), 'Characteristics of fentanyl overdose - Massachusetts, 2014-2016', *MMWR. Morbidity and Mortality Weekly Report*, 66(14), pp. 382–386. https://doi.org/10.15585/mmwr.mm6614a2

Sutter, M. E., Gerona, R. R., Davis, M. T., Roche, B. M., Colby, D. K., Chenoweth, J. A., Adams, A. J., Owen, K. P., Ford, J. B., Black, H. B. and Albertson, T. E. (2017), 'Fatal fentanyl: one pill can kill', *Academic Emergency Medicine*, 24(1), 106–113.

van der Schrier, R., Roozekrans, M., Olofsen, E., Aarts, L., van Velzen, M., de Jong, M., Dahan, A., Niesters M. (2017), 'Influence of ethanol on oxycodone-induced respiratory depression: A dose-escalating study in young and elderly individuals', *Anesthesiology*, 126(3), pp. 534–542.

Slovenian National Forensic Laboratory (2017), '4F-iBF (C23H29FN2O)'. Analytical report. European Project RESPONSE to challenges in forensic drug analyses. Available at: http://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/4F-iBF-ID-1710-16-report.pdf.

Swanson, D. M., Hair, L. S., Strauch Rivers, S. R., et al. (2017), 'Fatalities involving carfentanil and furanyl fentanyl: two case reports' (Abstract). 2017 SOFT-TIAFT Meeting, Boca Raton, FL, September 9–14, 2017. Programme book, p. 163.

SWGDRUG (2016), '4-Fluoroisobutyrylfentanyl'. Monograph, latest revision 15th November 2016. Available at: http://www.swgdrug.org/Monographs/4-Fluoroisobutyrylfentanyl.pdf

Tomassoni, J., Hawk, K. F., Jubanyik, K., Nogee, D. P., Durant, T., Lynch, K. L., Patel, R., Dinh, D., Ulrich, A. and D'Onofrio G. (2017), 'Multiple fentanyl overdoses - New Haven, Connecticut, June 23, 2016', *MMWR. Morbidity and Mortality Weekly Report*, 66(4), pp. 107–111.

Turri, J. L., Papsun, D. M., and Logan, B. K. (2017), 'Changes and trends in the novel illicit opioids use in 2016 and 2017 from a large postmortem population' (Abstract). 2017 SOFT-TIAFT Meeting, Boca Raton, FL, September 9–14, 2017. Programme book, p. 270.

Ujváry, I., Jorge, R., Christie, R., et al. (2017), 'Acryloylfentanyl, a recently emerged new psychoactive substance: a comprehensive review', *Forensic Toxicology*, 35(2), pp. 232–243.

United States Centers for Disease Control and Prevention (US CDC) (2013), Recommendations for laboratory testing for acetyl fentanyl and patient evaluation and treatment for overdose with synthetic opioid, 20 June 2013. https://emergency.cdc.gov/han/han00350.asp.

US CDC (2016), Fentanyl: Preventing occupational exposure to emergency responders, November 28, 2016. https://www.cdc.gov/niosh/topics/fentanyl/default.html

United States Drug Enforcement Administration (US DEA) (2017a), Fentanyl. A briefing guide for first responders. U.S. Drug Enforcement Administration. https://www.dea.gov/druginfo/Fentanyl_BriefingGuideforFirstResponders_June2017.pdf

US DEA (2017b), '4-Fluoroisobutyryl Fentanyl. Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5, and 6) for Temporary Scheduling. Drug and Chemical Evaluation Section, Office of Diversion Control, Drug Enforcement Administration, Washington, DC 20537. January 2017. Available at: https://www.regulations.gov/document?D=DEA-2017-0004-0002.

Watanabe, S., Vikingsson, S., Roman, M., et al. (2017), '*In vitro* and *in vivo* metabolite identification studies for the new synthetic opioids acetylfentanyl, acrylfentanyl, furanylfentanyl, and 4-fluoro-isobutyrylfentanyl', *AAPS Journal*, 19(4), pp. 1102–1122.

White, J. M. and Irvine, R. J. (1999), 'Mechanisms of fatal opioid overdose', *Addiction*, 1999, 94(7), 961–972. https://doi.org/10.1046/j.1360-0443.1999.9479612.x

World Health Organisation (WHO) (2017), '4-Fluoroisobutyrfentanyl (4-FIBF). Review report agenda item 4.9.' Expert Committee on Drug Dependence Thirty-ninth Meeting, Geneva, 6-10 November 2017. Available at: http://www.who.int/medicines/access/controlled-substances/Critical_Review_4FIBF.pdf.

Zaney, M. E., Shoff, E. N., Hime, G. W., et al. (2017), 'Detection of U-47700 in blood and drug paraphernalia from postmortem cases' (Abstract). 2017 SOFT-TIAFT Meeting, Boca Raton, FL, September 9–14, 2017. Programme book, p. 85.

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| EMCDDA-Europol Joint Report on a new psychoactive substance N-(4-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)isobutyramide, 2018 www.emcdda.europa.eu/publications/joint-reports/4f-ibf

| EMCDDA–Europol 2016 Annual Report on the implementation of Council Decision 2005/387/JHA, Implementation reports, 2017 www.emcdda.europa.eu/publications/implementation-reports/2016

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