Council of the European Union

Brussels, 28 February 2017
(OR. en)

6788/17

CORDROGUE 30
SAN 78
ENFOPOL 92

NOTE

From:	EMCDDA
To:	Delegations
No. prev. doc.:	15562/16
Subject:	Risk assessment report on a new psychoactive substance: *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl)

Following the Council's request to conduct a Risk Assessment on a new psychoactive substance, N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide (acryloylfentanyl), the EMCDDA hereby presents the above-mentioned Risk Assessment Report drawn up by its Scientific Committee pursuant to Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances.

ANNEX

Risk assessment report on a new psychoactive substance:
***N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl)**

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

Contents

1. Introduction

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (commonly known as acryloylfentanyl or acrylfentanyl). 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 acryloylfentanyl, is provided below.

([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

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

Acryloylfentanyl was formally notified on 7 July 2016 by the EMCDDA on behalf of the Danish National Focal Point, in accordance with Article 4 of the Council Decision. The notification related to the seizure of a capsule made on 11 May 2016 by the Department of Forensic Psychiatry, Aalborg Psychiatric Hospital, Aalborg. Following an assessment of the available information on acryloylfentanyl, and in accordance with Article 5 of the Council Decision, on 17 November 2016 the EMCDDA and Europol submitted a *Joint Report* on acryloylfentanyl ([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 23 January 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'.

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

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

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

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

([6]) EMCDDA and Europol (2016), EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl), EMCDDA, Lisbon. Available at: http://emcdda.europa.eu/publications/joint-reports/acryloylfentanyl

In accordance with Article 6.2, the meeting to assess the risks of acryloylfentanyl was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of two additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of acryloylfentanyl, 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 22 February 2017 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMA. A list of the extended Scientific Committee, as well as the list of other participants attending the risk assessment meeting, is annexed to this report (Annex 2).

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

- Technical report on *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl) (Annex 1);
- EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl) ([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 meeting by the participants;
- The EMCDDA operating guidelines for the risk assessment of new psychoactive substances ([1]); and,
- Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ([2]).

Finally, it is important to note that this risk assessment report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with acryloylfentanyl. 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 constitutes a central component of the EU Early Warning System, has also been strengthened resulting in more information being available regarding serious adverse events associated with new psychoactive substances. Nonetheless, it is likely that these events remain under-detected and under-reported.

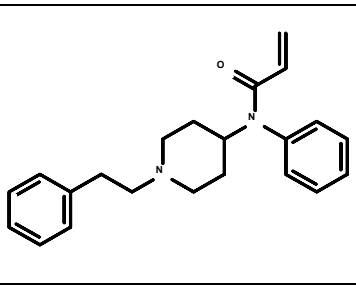
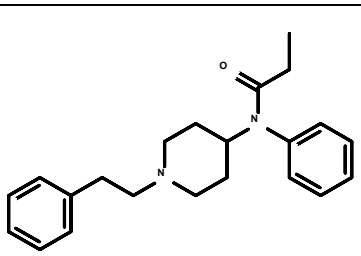
2. Physical, chemical and pharmacological description

N-(1-Phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl) is an acrylamide derivative of 4-anilinopiperidine and is an unsaturated analogue of fentanyl, which is a propionamide (Figure 1). Acryloylfentanyl contains one basic nitrogen atom in the piperidine ring readily forming salts with organic or inorganic acids. All the fentanyl derivatives have in common an aryl group linked to a 4-*N*-acetylanilinopiperidine.

Acryloylfentanyl is known from the scientific literature and is a close structural relative of fentanyl. Fentanyl is a fast but short-acting synthetic opioid that has been widely used in clinical practice including as an adjunct to general anaesthesia during surgery and for postoperative pain management. Acryloylfentanyl is also structurally related to acetylfentanyl, which was the subject of an EMCDDA–Europol Joint Report in 2015 following more than 30 deaths in Europe.

Pharmacologically, acryloylfentanyl is an opioid.

Figure 1. The molecular structure, molecular formula and molecular mass of acryloylfentanyl compared to fentanyl.

		
	acryloylfentanyl	fentanyl
Molecular formula	$C_{22}H_{26}N_2O$	$C_{22}H_{28}N_2O$
Molecular mass	334.46	336.48

Synthetic opioids like fentanyl and related 4-anilinopiperidine derivatives are potent analgesics. Initially developed in the 1960's, a small number of this family of compounds — alfentanil, fentanyl, sufentanil and remifentanil — are 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 tablets, transdermal patches, lozenges, liquid for injection and nasal sprays. Some are also used in veterinary medicine as general anaesthetics, to immobilise large animals, and for pain management.

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 fourteen fentanils are currently scheduled under the 1961 Single Convention on Narcotic Drugs.

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

Similar to other fentanils, several synthetic routes to produce acryloylfentanyl are available in the scientific literature and have been published on the internet. Most of these are straightforward, make use of common laboratory equipment and precursors, and require only basic knowledge of chemistry. However, due to the high potency of acryloylfentanyl there is a serious risk of severe poisoning following accidental exposure during its manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substance.

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

In Europe, acryloylfentanyl has usually been seized as a liquid — sold in ready-to-use nasal spray solutions which are typically unlabelled — and as a powder. It has also been seized as tablets.

The analytical identification of acryloylfentanyl in physical and biological samples is possible using several analytical techniques.

Immunoassays tests developed for morphine-type opioids are unlikely to give positive responses to acryloylfentanyl; while there is no information on whether acryloylfentanyl will give positive responses to immunoassays developed for fentanils. There is no information on the reaction of acryloylfentanyl to presumptive colour tests. The analytical identification of acryloylfentanyl should be made using techniques for which analytical data has been established: FT-IR, ^{1}H and ^{13}C NMR, DEPT and two dimensional NMR (COSY and HSQC) and GC-MS and QTOF-MS ([7]).

The availability of analytical reference material is important for correct identification and for facilitating the quantification of acryloylfentanyl 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 range.

([7]) FT-IR: Fourier transform infra-red; 1H and 13 C NMR: hydrogen-1 and carbon 13 nuclear magnetic resonance; DEPT: Distortionless enhancement by polarization transfer; COSY: Homonuclear correlation spectroscopy; HSQC: Heteronuclear single quantum correlation; GC-MS: Gas chromatography–mass spectrometry; EI: Electron ionization; QTOF: Quadrupole Time of Flight.

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

Route of administration and dosage

Acryloylfentanyl can be administered orally as a powder, as tablets, or as a solution; it can also be administered intranasally or sublingually *via* spray or snorted (insufflated); inhaled by vaporising e-liquid type solutions ('vaping'); inhaled by smoking or vaporising the 'free base'; administered transdermally, and injected.

In the acute intoxications suspected to involve acryloylfentanyl that were reported to the EMCDDA, the most common route of administration was intranasally using a nasal spray. Less commonly, snorting of powder or crushed tablets, oral administration of tablets, and injection of a 'nasal solution' were also reported.

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

Analysis of the concentration of nasal spray solutions of acryloylfentanyl in Sweden suggests that 10 mL nasal spray bottles have been sold containing 20 mg of the substance; one actuation (spray) would appear to deliver a dose of 0.2 mg. However, given that a range of different products appear to have been sold, caution should be taken in generalising these findings.

For nasal sprays, doses of 0.0027 mg to 0.2 mg were reported on user websites.

Pharmacology

Data on the pharmacology of acryloylfentanyl are limited to studies investigating its functional activity at opioid receptors *in vitro*, and its anti-nociceptive properties in mice.

An *in vitro* study shows that the affinity of acryloylfentanyl for opioid receptors is similar to that of fentanyl, and somewhat greater than that of morphine. *In vivo* studies suggest that acryloylfentanyl is a more potent and longer lasting anti-nociceptive agent than fentanyl, and that it has a time-response profile more closely related to that of morphine. At comparable doses, the analgesic effect of fentanyl became insignificant at 90-120 minutes, whilst acryloylfentanyl maintained analgesia for this same time period. Administration of naloxone reversed the antinociceptive activity of acryloylfentanyl *in vivo*, however, this effect was transient and analgesia from acryloylfentanyl returned after a period of time.

Acryloylfentanyl, as part of a series of compounds, was studied as a potential covalent receptor affinity label; the available data suggests that acryloylfentanyl does not cause irreversible binding to opioid receptors (at least in rodents).

There are no published studies on the pharmacokinetics of acryloylfentanyl. Due to its lipophilicity, acryloylfentanyl, like fentanyl, is expected to readily cross the blood-brain barrier and also diffuse into fat and other tissues and is thus likely to have a large volume of distribution. In addition, the pharmacokinetics and the metabolic pathway of acryloylfentanyl are expected to be similar to that of fentanyl or acetylfentanyl. As such, acryloylfentanyl could be predicted to undergo metabolism by hepatic CYP450 3A4 and CYP450 3A5 isoenzymes.

It is expected that one of the main metabolites present in biological matrices is the 'desphenethyl' derivative of acryloylfentanyl, that is 'acryloyl norfentanyl'. Amide hydrolysis (deacylation) is a minor pathway for fentanyl and probably an insignificant biotransformation for the acryloyl analogue. Terminal hydroxylation of the acyl chain, which is also a minor biotransformation step for fentanyl in humans, produces what is often called 'hydroxyfentanyl' but such a hydroxylation cannot take place in case of acryloylfentanyl.

There is some information on the biological activity of two potential metabolites of acryloylfentanyl. An *in vitro* study assessing the opioid-like activity of several fentanyl metabolites found that *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) and 4-anilinopiperidine were less potent than either morphine or fentanyl by several orders of magnitude. The only metabolite showing significant activity in this study was a phenolic derivative hydroxylated at the 4-position of the phenylethyl moiety of fentanyl, the activity of which was found to lie between morphine and pethidine. This implies that the corresponding phenolic metabolite of acryloylfentanyl, if formed, may have some level of opioid activity and thus may contribute to the biological, including toxicological, properties of the parent substance. No information was found in the published literature regarding two other potential metabolites of acryloylfentanyl: the desphenethyl derivative of acryloylfentanyl and nor-acryloylfentanyl.

Inter-individual genetic variability in metabolising enzymes

There is no information on the inter-individual genetic variability in metabolising enzymes for acryloylfentanyl.

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

Should acryloylfentanyl be metabolised by CYP450 3A4 and CYP450 3A5 isoenzymes, then the use of this substance with strong or moderate inhibitors of these isoenzymes (such as ketoconazole, fluconazole, clarithromycin, erythromycin, indinavir, ritonavir and saquinavir) may result in increased plasma concentration of acryloylfentanyl which could be toxicologically significant. Overall, this could increase the risk of poisoning including potentially fatal respiratory depression.

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

The use of fentanyl with 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 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 acryloylfentanyl.

Severe and unpredictable potentiation by MAOIs has been reported with opioid analgesics.

Similar to fentanyl, the use of partial opioid agonists/antagonists (such as buprenorphine, nalbuphine, pentazocine) which have high affinity to opioid receptors but relatively low intrinsic activity could partially antagonise the effects of acryloylfentanyl and may induce withdrawal symptoms in people who are opioid dependent.

Psychological and behavioural effects

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

Legitimate uses

Acryloylfentanyl has no established or acknowledged medical value or use (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for acryloylfentanyl in the European Union nor in the Member States that responded to the information request from the European Medicines Agency (EMA) that was launched under Article 5 of the Council Decision. In addition, there is no information to suggest acryloylfentanyl is used for the manufacture of a medicinal product or an active pharmaceutical ingredient (API) of a medicinal product in the European Union. It should be noted that there is no European Union database on the synthetic routes of all registered medicinal products.

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

3. Chemical precursors that are used for the manufacture

Information on the chemical precursors and the synthetic methods employed for acryloylfentanyl detected on the drug market within the European Union is limited. Impurities detected in a seizure suggest that 4-ANPP may be used as a precursor and triethylamine as an acid scavenger during the synthesis.

The manufacture of acryloylfentanyl 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 acryloylfentanyl. A one-step method uses 4-ANPP and propionyl chloride, both of which are readily available, for the manufacture of the substance. Other acylation methods that use an activated ester of acrylic acid can also be used. Use of a different acylating agent in the final acylation step could provide other fentanils.

The potential precursors of acryloylfentanyl are 4-ANPP, 1-(2-phenylethyl)piperidin-4-one (NPP), acryloyl chloride, 3-chloropropionyl chloride, *N*-phenyl-*N*-(piperidin-4-yl)acrylamide and phenethyl halide. None of these precursors are included in Table I or Table II of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.

Theoretically, acryloylfentanyl could serve as a precursor for the production of the internationally controlled fentanyl.

4. Health risks

Individual health risks

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

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

Acryloylfentanyl may be used in combination with other drugs (intentionally or unintentionally). Information from the seizure of nasal sprays containing acryloylfentanyl show that these are typically sold as unlabelled bottles. In some cases users have also filled nasal sprays previously containing medicinal products with acryloylfentanyl. The lack of instructions and potential for accidental use by others poses an inherent risk of poisoning.

Limited data from seizures have shown that it may be encountered in combination with heroin and carfentanil or sold as other drugs such as fentanyl. Therefore, some users are unlikely to be aware of the exact substance(s) being ingested (by whatever route). This presents an inherent risk to the individuals.

Acryloylfentanyl is available as ready-to-use nasal sprays which typically contain milligram amounts of dissolved substance. The preparation of solutions containing milligram amounts of substance is inherently prone to mistakes in weighing and dilution which may lead to solutions with higher (or lower) concentrations. This may constitute an increased risk of acute toxicity to the individuals, which are unlikely to be able to control the exact dose of acryloylfentanyl being consumed.

Acute toxicity

The acute toxicity of acryloylfentanyl has been assessed in mice in one study which suggests that its acute toxicity is similar to that of fentanyl.

No studies were identified that have investigated the acute effects of acryloylfentanyl and/or its metabolites in humans. For fentanyl the estimated lethal dose in humans could be as low as 2 mg when injected intravenously.

Acute intoxications

Twenty-one acute intoxications suspected to involve acryloylfentanyl were reported to the EMCDDA by Sweden. These related to acute poisoning presentations to hospital emergency departments reported to the Swedish Poison Information Centre. They were not analytically confirmed in biological samples.

Where known, acryloylfentanyl was usually administered intranasally using nasal sprays. To a lesser extent powders or crushed tablets were snorted or tablets taken orally. In one case a nasal solution was injected.

Of the acute intoxications, 18 (86%) were male; 3 (14%) were female. The mean age of the male cases for which an age was known was 35 years (median 29) and ranged from 22 to 44 years (n=7); for the female cases the ages were 22, 23, and 40 years. All 21 cases required treatment in hospital. Thirteen (62%) were classified by the poison centre as life-threatening and 8 were classified as non-life threatening. Use of the antidote naloxone was reported in 8 of the cases, with apparent reversal of the poisoning reported in 4 of these cases. In 10 cases it was reported that the patient recovered; the outcome was unknown in the remaining 11 cases.

Reported clinical features included: miosis, unconsciousness, and respiratory depression; tachycardia, somnolence, restlessness, and nausea/vomiting were also reported. However, the lack of analytically confirmed drugs hinders the interpretation of this as other drugs may have caused or contributed to the symptoms observed. Nevertheless, such symptoms would be consistent with poisoning from an opioid, including a fentanil.

Deaths

A total of 47 deaths were reported by 3 Member States: Denmark (1), Estonia (3) and Sweden (43). In all cases, acryloylfentanyl was analytically confirmed from post-mortem samples. No further information was available regarding the deaths in Estonia, and therefore these have been excluded in the analysis below.

The 44 deaths reported by Denmark and Sweden occurred between April and December 2016; with more than 70% occurring in a three month period between June and August 2016.

Of these deaths, 38 were male (86%) and 6 were female (14%). The mean age of the males was 31 years (median 29) and ranged from 19 to 54 years; the mean age of the females was 42 years (median 43) and ranged from 29 to 50 years.

Circumstances and cause of death

In all deaths there was a lack of information regarding any symptoms experienced by the deceased prior to death.

In more than 70% of the cases, the individuals were found dead or died in a home environment (their own or someone else's). Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxications); however, in 3 cases the deceased were described as being unconscious prior to death, and in 1 of these cases it was reported that the deceased lost consciousness 10 minutes after using acryloylfentanyl.

The cause of death was available in 43 out of 44 cases. In at least 40 deaths, acryloylfentanyl was either the cause of death or is likely to have contributed to death (even in presence of other substances); in 2 of these deaths acryloylfentanyl was the sole substance detected. Six deaths were potentially suicidal in nature.

Acryloylfentanyl was quantified in all cases. Post-mortem blood concentrations between 0.01 and 5.0 ng/g blood were recorded.

A range of other substances were detected in 42 of the 44 deaths, including: benzodiazepines, zopiclone, gabapentinoids (pregabalin and gabapentin), ethanol, cannabinoids (including synthetic cannabinoids), synthetic cathinones, amphetamines, antidepressants, and antipsychotics. In 38 of the deaths, acryloylfentanyl was the only opioid detected. In the remaining 6 cases, buprenorphine (2 deaths), oxycodone (1); oxycodone and hydrocodone (1); oxycodone and 4-fluoro-isobutyrfentanyl (1); and, 4-chloro-isobutyrfentanyl (1) were detected. Due to their potency and associated analytical challenges, the presence of some other fentanils (e.g. carfentanil) cannot be completely excluded.

Overall, whilst other substances may have contributed some toxicity, a synergistic effect with acryloylfentanyl would have been likely (e.g. other central nervous system depressants such as ethanol, benzodiazepines, opioids, etc.). Nevertheless, the potent opioid nature of acryloylfentanyl means the primary toxic contribution could be attributed to the drug and death may not have occurred if acryloylfentanyl had not been used.

Ability to operate machinery and drive

There have been no studies of the effects of acryloylfentanyl on the ability to drive and operate machines. 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 acryloylfentanyl.

Chronic toxicity

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

Abuse liability and dependence potential

There have been no studies that have investigated the dependence and/or abuse potential of acryloylfentanyl in animals or humans. Given what is currently known about the pharmacology of acryloylfentanyl, it is reasonable to assume that the substance has both a potential for abuse and dependence. Further research will be required in order to determine such effects.

Public health risks

The public health risks associated with acryloylfentanyl 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 acryloylfentanyl are not available. In addition, risk of accidental exposure needs to be considered.

Extent, frequency, and patterns of use

The available data suggests that acryloylfentanyl is sold online in small and wholesale amounts as a ‘research chemical, typically as a powder and as ready-to-use nasal sprays. Acryloylfentanyl may also be sold on the illicit opioid market, as suggested by seizures where it was found in mixtures with heroin and carfentanil. In these cases, it is reasonable to assume that some individuals may not be aware that they are consuming acryloylfentanyl.

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

Based on its pharmacological effects and that it is sold as a ‘legal’ replacement to illicit opioids, it would be expected that acryloylfentanyl could be sought by those looking for substitutes to opioids, such as prescription opioids and heroin. It also appears that there is interest in this substance by some psychonauts.

Availability and quality on the market

While discussions on user websites suggest that acryloylfentanyl may have been available since 2014, the first analytical detection reported in Europe occurred in Denmark in May 2016. The most recent detection reported occurred in January 2017.

A total of 162 seizures have been reported by 5 Member States. The seizures occurred mostly at street-level as a powder (totalling 113 grams) or a liquid (totalling 1495 mL). While these quantities may appear relatively small they should be considered in the context of the high potency of acryloylfentanyl.

Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviours of users of acryloylfentanyl.

Some users may be experimenting with this opioid by means of ready-to-use preparations; whilst others may seek to self-medicate pain or opioid-withdrawal symptoms. Some users, particularly those consuming acryloylfentanyl in mixtures with other illicit opioids such as heroin may not be aware that they are consuming the substance.

Data from the acute intoxications suspected to involve acryloylfentanyl shows that the most common route of administration were nasal sprays.

Data from user websites and deaths reported to the EMCDDA suggests that, similar to other opioids, acryloylfentanyl is typically used in the home environment.

Of note is that information from the deaths reported to the EMCDDA highlights that use of other opioids was uncommon; while polydrug use was common, including the use of other CNS depressants such as benzodiazepines, pregabalin, gabapentin and ethanol.

Nature and extent of health consequences

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

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

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

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

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

In the past two years a number of mass poisoning events over a short time period caused by fentanils have been reported particularly in the United States and Canada. These types of outbreaks have had the potential to overwhelm emergency departments and deplete stocks of naloxone. Stocks and availability of the naloxone, as well as adequacy of training in how to resuscitate poisoned patients both in clinical and community settings may need to be assessed. This might include a review of the availability of naloxone to users through take-home naloxone programmes.

Accidental exposure of acryloylfentanyl and other fentanils — such as skin contact, inhalation, or ingestion — also poses a serious risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel as well as custodial settings and postal services. In addition to exercising extreme caution when handling materials suspected to contain fentanils, working environments and personnel should be equipped with appropriate protective equipment. The antidote naloxone should be readily available to personnel in sufficient quantities; training in resuscitation and naloxone administration should also be available.

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

Long-term consequences of use

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

Conditions under which the substance is obtained and used

Based on the available data, it appears that one particularly important source of acryloylfentanyl was ready-to-use nasal sprays sold on the surface web in Sweden. This is also reflected in acute intoxications, where acryloylfentanyl was usually administered by nasal sprays.

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

Overall, acryloylfentanyl may be directly sought by some users, whilst others, such as those that purchase it at street-level, may be unaware that they are using acryloylfentanyl.

5. Social risks

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

Individual social risks

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

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

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

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

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

As discussed above, accidental exposure of acryloylfentanyl and other fentanils — such as skin contact, inhalation, or ingestion — also poses a serious risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel as well as custodial settings and postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in resuscitation and adequate provision of naloxone to reverse poisoning.

Economic costs

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

Possible appeal to specific population groups

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

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

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

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

Estonia and Sweden informed Europol that acryloylfentanyl was ordered in powder form from companies based in China. According to information from Swedish Police, the substance is then used to create ready-to-use unlabelled nasal spray products, with the nasal sprays also purchased from vendors in China. Swedish Police also reported that the open sale of fentanils on the internet appeared to generate large profits for retailers.

7. Information on any assessment in the United Nations system

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs of 1961 and the Convention on Psychotropic Substances of 1971. At the time that the Joint Report was prepared ([6]), the World Health Organization informed the EMCDDA that acryloylfentanyl was not currently under assessment nor had it been under assessment by the United Nations system.

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

Nine Member States (Cyprus, Denmark, Estonia, Finland, Ireland, Latvia, Lithuania, Sweden, and the United Kingdom) and Turkey reported that acryloylfentanyl is controlled under drug control legislation.

- In Cyprus, acryloylfentanyl is controlled within the context of a generic clause which addresses fentanyl chemical groups.

- In Denmark, acryloylfentanyl was included in an amendment of the Executive Order on Euphoriant Substances which entered into force on 24 November 2016.

- In Estonia acryloylfentanyl is controlled by way of generic definition.

- In Finland, acryloylfentanyl is controlled as a narcotic as of 14 November 2016.

- In Ireland, acryloylfentanyl is controlled under the Misuse of Drugs act 1977 (Schedule 1 (d) (iv), S.I. 251 of 1987) by way of a generic definition.

- In Latvia, acryloylfentanyl 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, acryloylfentanyl is controlled as of 12 January 2017 by the Minister of Health Order No V-22.

- In Sweden, acryloylfentanyl has been regulated as a narcotic since the 16 August 2016.

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

- In Turkey, acryloylfentanyl is controlled under Drug Law on Drugs numbered 2313 with the decree of Council of Ministers 2016/9712 dated 27 December 2016.

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

- In Austria, acryloylfentanyl may be covered by the Austrian Act on New Psychoactive substances due to the presence of a phenethylamine moiety in the structure of the substance ([8]).

([8]) Austria reported that 'Due to its phenethylamine [sic] structure acryloylfentanyl is unintentionally covered by the Austrian Act on New Psychoactive substances – but some experts might see it differently (https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=20007605)'.

- In Poland, acryloylfentanyl is controlled according to the general definition of the 'substitute drug' which has been included to the 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). Article 44b of the above mentioned Act bans manufacturing or introducing substitute drugs to trade.

In Norway, the importation of, trade in and marketing of acryloylfentanyl is controlled by the Medicines Act.

Seventeen Member States (Belgium, Bulgaria, Croatia, Czech Republic ([9]), France, Germany, Greece, Hungary, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain) reported that acryloylfentanyl is not subject to control measures at the national level.

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

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

Relevant to these discussions is that around the time that acryloylfentanyl was subject to control measures in Sweden there was a marked decrease in the number deaths associated with the substance. In addition, in February 2017 it was announced that acryloylfentanyl will be controlled in China as of the 1 March 2017. This control measure may at least deter the open manufacture and sale of this substance by chemical companies, which are linked to the supply of the substance in Europe.

([9]) The Czech Republic reported that an amendment of the Government Regulation No. 463/2013 Coll. is currently in process.

There are no studies on the possible consequences of such control measures on acryloylfentanyl. 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 acryloylfentanyl 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 acryloylfentanyl 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. Of relevance here is that since acryloylfentanyl was first notified in May 2016, a further seven new fentanils have been detected on the drug market in Europe.

- This control option could create an illicit market in acryloylfentanyl 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 acryloylfentanyl 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 acryloylfentanyl on the market post-control, should this control option be pursued.

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

10. Conclusion

N-(1-Phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl) is a synthetic opioid and is structurally similar to fentanyl, a controlled substance widely used in medicine as an adjunct to general anaesthesia during surgery and for pain management. The available data suggests that acryloylfentanyl is a potent and long-lasting antinociceptive agent acting on the opioid system.

While the acute toxicity of acryloylfentanyl has not been determined, observations from a study conducted in mice suggest that it is similar to fentanyl. Its high potency constitutes a considerable risk of acute toxicity through respiratory depression.

Acryloylfentanyl has been available in Europe since at least April 2016 and has been detected in 6 Member States. The detected quantities are relatively small; however, they should be considered in the context of the high potency of acryloylfentanyl.

Acryloylfentanyl 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 acryloylfentanyl may have also been sold on the illicit opioid market.

Typically, the substance has been administered by nasal spray, orally, and by nasal insufflation. But other routes of administration, including injecting, vaping, and transdermal administration have been reported.

Concerns exist over ready-to-use nasal sprays and e-liquids for vaping which are novel ways of administering the drug, and which may have the potential to make the use of fentanils easier (with similar effects to injecting) and more socially acceptable.

More than twenty acute intoxications suspected to be due to acryloylfentanyl have been reported. The clinical features were generally consistent with opioid-like toxicity and included life-threatening effects.

Clinical experience suggests that naloxone works as an antidote to poisoning caused by acryloylfentanyl and it is likely that repeated doses are required.

Forty-seven deaths have been reported by 3 Member States where acryloylfentanyl was detected post-mortem. In the majority of cases other drugs were also detected with acryloylfentanyl. In at least 40 deaths, acryloylfentanyl was either the cause of death or is likely to have contributed to death.

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

There is no information to suggest the involvement of organised crime in the manufacture, distribution (trafficking) and supply within the European Union. There is limited information on the chemical precursors and the synthetic routes used to manufacture the acryloylfentanyl 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. The available data suggests that most of the acryloylfentanyl on the market in Europe has been produced by chemical companies based in China.

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

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

Nine Member States and Turkey control acryloylfentanyl under drug control legislation and two Member States and Norway control acryloylfentanyl under other legislation.

As for any new psychoactive substance, many of the questions related to acryloylfentanyl 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 acryloylfentanyl 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 acryloylfentanyl 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 acryloylfentanyl. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, since 2016 at least seven fentanils and a number of other new opioids that may replace acryloylfentanyl 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 acryloylfentanyl to users, practitioners, policy makers, decision makers and those who may be at risk of accidental exposure An additional challenge in respect to reducing risk in users and potential users, is the balance between providing information to prevent harm and the unintended consequences of communicating the risks of opioids. There is evidence that using terms to describe them as 'potent', 'strong', 'deadly', and 'toxic' can lead some individuals to specifically seek out these substances. Such unintended promotion of the substances may also extend to former users and other groups.

11. List of annexes

Annex 1: Technical report on *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl).

Annex 2: List of participants at the risk assessment meeting of *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl).

ANNEX I

Technical report on *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl)

24 February 2017

Annex 1 to the Risk assessment report on *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl).

Table of contents

Introduction

In order to prepare for a risk assessment that has been convened under the Council Decision 2005/387/JHA 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 for drafting a technical report.

This technical report has been prepared for the risk assessment of *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl) that will be held at the EMCDDA premises in Lisbon on Wednesday 22 February 2016.

Some of the sections in this report were prepared under EMCDDA contract (ref. CT.16.SAT.0099.1.0 and CT.16.SAT.0100.1.0).

It is important to note that when interpreting the information on self-reported user experiences that is provided 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. In addition, the information provided on user websites may not necessarily be representative of other users of acryloylfentanyl and should be regarded as illustrative only.

Given the time frame stipulated in the Council Decision, the technical report has not been formally edited by the EMCDDA. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The risk assessment report on a new psychoactive substance: *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl) to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

Reported prepared by

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Acknowledgements

The EMCDDA would like to thank the following for their contribution in producing this report:

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

([10]) Budapest University of Technology and Economics, Hungary.
([11]) Alere Forensics, Worcester, United Kingdom.
([12]) EMCDDA.

- the Europol national units (ENUs) and Europol Project Synergy;

- Veronika Mikes for her assistance in interpreting the Chinese articles used in this report;

- Dr Anders Helander, Department of Laboratory Medicine and Department of Clinical Pharmacology, Karolinska Institutet, Stockholm;

- Dr Torben Breindahl, Department of Clinical Biochemistry, North Denmark Regional Hospital, Aalborg University, Hjørring.

Data sources

The information in this technical report is derived from:

- data reported by the Member States, Turkey and Norway to the EMCDDA and Europol in accordance with Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances ([13]); 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 acryloylfentanyl.

Search strategy

Literature searches used both chemical structure and text queries in online databases; searches were conducted between September 2016 and February 2017. The retrieved publications were then scanned for additional relevant references (snowballing technique).

Chemical structure-based searches were done in SciFinder® (American Chemical Society, Chemical Abstract Service) and Reaxys® (Elsevier) databases using both the exact structure and the substructure of acryloylfentanyl (for the latter, substitutions on the phenyl, phenylethyl and piperidine moieties were allowed but the terminal propenamide group was defined by –CH=CH2 with explicit H-atoms. Structural searches in SureChEMBL patent database retrieved no relevant hits.

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

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), *ScienceDirect* (Elsevier), in popular English-language drug forums and in *Google* and *Twitter*. The search term used were: 'acryloylfentanyl', 'acryl fentanyl', 'acryl fentanyl', 'fentanyl acroyl analog', 'fentanyl propenamide', 'Acr-F opioid', 'Akrylfentanyl' as well as for the following Chemical Abstract Service Registry Numbers ([14]): 82003-75-6, and 79279-03-1.

Textual searches for 'acryloylfentanyl' and 'acryloylfentanyl' in *Scopus*® and *Ovid*® databases retrieved no relevant hits.

The Internet was also searched in Google for the molecular formula string 'C22H26N2O'.

In addition, reviews and selected papers from the vast literature on fentanyl, the close structural relative of acryloylfentanyl, were also consulted as were results of papers and patents retrieved by substucture searches in *SciFinder*® and *Reaxys*®.

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

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

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

N-(1-Phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl) is an acrylamide derivative of 4-anilinopiperidine and is an unsaturated analogue of fentanyl, which is a propionamide (Figure 1). Acryloylfentanyl contains one basic nitrogen atom in the piperidine ring readily forming salts with organic or inorganic acids. All the fentanyl derivatives have in common an aryl group linked to an 4-*N*-acetylanilinopiperidine.

Acryloylfentanyl is a close structural relative of fentanyl ([15,16]) which is a fast but short-acting synthetic opioid that has been widely used in clinical practice as an adjunct to general anaesthesia during surgery and for pain management.

([14]) CAS RNs are especially useful for conducting searches for online vendors of any substance because it overcomes nomenclatural and language limitations.
([15]) http://www.emcdda.europe.eu/publications/drug-profiles/fentanyl
([16]) Fentanyl is included in Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol.

Acryloylfentanyl is also structurally related to acetylfentanyl, which was the subject of an EMCDDA–Europol Joint Report in 2015 following more than 30 deaths over a short period of time (EMCDDA & Europol, 2015).

Acryloylfentanyl is known from the scientific literature only.

Pharmacologically, acryloylfentanyl is an opioid.

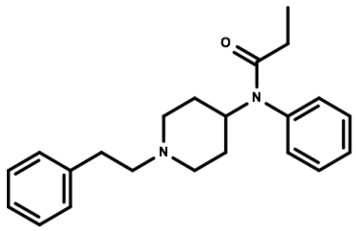
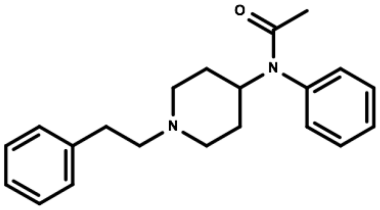
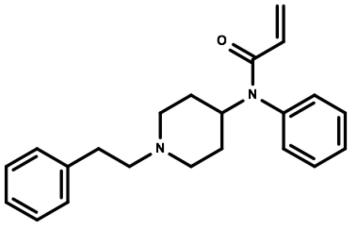
Fentanyl and congeners were first disclosed in patents by the Belgian company Research Laboratorium Dr. C. Janssen in the early 1960s (Janssen and Gardocki, 1964; Janssen, 1965; see also Janssen, 1962). Neither acryloylfentanyl nor any other unsaturated amides were claimed in the original patents. The synthesis and antinociceptive activity of acryloylfentanyl were first described in 1981 (Zhu et al., 1981).

Fentanyl analogues first emerged on the illicit drug market in the United States of America in 1979; in fact, the term 'designer drugs' was specifically coined for these substances which at the time were not controlled under drug legislation (Henderson, 1988) ([17]). While acryloylfentanyl was not detected, its side-chain methylated homologue, that is α-methyl-acryloylfentanyl ([18]), was identified in samples along with α-methyl-acetylfentanyl (Anonymous, 1983; Clark and Nelson, 1984; Cooper et al., 1986).

([17]) Of note is that Henderson coined the term specifically to convey a number of novel characteristics related to the appearance of the fentanils on the drug market: '"I am probably going to be haunted by that until the day I die," he says. "It sounds like I am trivializing it, but I am not. We were getting samples that ranged from a pure white powder sold as China White to an off-white powder to a dark brown material that looked like Mexican Brown heroin. We got samples that were cut with heroin, and I wondered why someone would do that. It turns out that can help an addict get on a methadone program. The entire packaging and marketing concept to me was a designer phenomenon. Additionally, you could literally design the potency and duration of action into the molecule"' (Baum, 1985).

([18]) Its names: *N*-phenyl-*N*-[1(1-phenylpropan-2-yl)piperidin-4-yl]prop-2-enamide, *N*-phenyl-1-(1-phenylpropan-2-yl)acrylamide, *N*-[1-methyl,2-phenylethyl)-4-piperidyl]acrylanilide, or □-methyl-acrylfentanyl; The CAS RN is unknown. Note: in the widely used *Designer Drugs Directory* (Valter and Arrizabalaga, 1998) the CAS RN 79297-03-1 given for acryloyl-□-methylfentanyl is erroneous: this number in fact denotes acryloylfentanyl hydrochloride (see above).

Figure 1: The molecular structure, molecular formula and molecular mass of fentanyl (left), acetylfentanyl (centre), and acryloylfentanyl (right).

Fentanyl	**Acetylfentanyl**	**Acryloylfentanyl**
		
$C_{22}H_{28}N_2O$	$C_{21}H_{26}N_2O$	$C_{22}H_{26}N_2O$
336.48	322.44	334.46

Fourteen fentanyl derivatives are controlled under the 1961 United Nations Single Convention on Narcotic Drugs (Schedule I and IV): 3-methylfentanyl, 3-methylthiofentanyl, acetyl-alpha-methylfentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, para-fluorofentanyl, thiofentanyl and acetylfentanyl. Alfentanil, fentanyl, sufentanil and remifentanil are controlled under Schedule I. The controls on acetylfentanyl entered into force on 18 May 2016.

Names and other identifiers

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

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

Other names: *N*-(1-phenethylpiperidin-4-yl)-*N*-acroylanilinopiperidine; *N*-(1-phenylethylpiperidin-4-yl)-*N*-phenylacrylamide, enfentanyl (Essawi, 1998).

Commonly used names: acryloylfentanyl or acrylfentanyl

Chemical Abstract Service Registry Numbers (CAS RNs) ([19,20])

82003-75-6 free amine

79279-03-1 hydrochloride salt

PubChem SID: 144091883 ([21])

IUPAC International Chemical Identifier Key (InCHI Key):22 RFQNLMWUIJJEQF-UHFFAOYSA-N

Street names: acryloyl-F, Acr-F, ACF ([23])

Identification and analytical profile

Acryloylfentanyl appears to be mentioned first on a Swiss website on 20 January 2014 (Eve&Rave, 2014) ([24]). On 5 April, 2016, a picture of a nasal spray formulation was posted in Swedish on Twitter ([25]).

Acryloylfentanyl was first detected as powder in a capsule seized in Denmark on 11 May 2016 and reported to the EMCDDA on 16 June 2016 (EMCDDA & Europol, 2016; Breindahl et al., 2016).

Vendors on the surface web and darknet market places have offered acryloylfentanyl as light green or brown to light brown powders or as 'pellets' ([26]); the purity is usually claimed to be >99%. In addition, it has also been sold on the surface web in Sweden as ready-to-use nasal spray solutions; typically these are unlabelled.

([19]) The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.

([20]) An internet vendor (http://drugspowerstore.com) gives CAS RN 21406-26-7 for acrylfentanyl but this number is actually the CAS RN of *N*-phenyl-1-(2-phenylethyl)piperidine-4-amine (also called 4-ANPP in short), the precursor of several fentanyl analogues.

([21]) https://pubchem.ncbi.nlm.nih.gov/substance/144091883 (created 15 September 2012)

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

([23]) Not to be confused with 'AF', which is one of the street names for acetylfentanyl (EMCDDA & Europol, 2015).

([24]) http://www.eve-rave.ch/Forum/viewtopic.php?f=101&t=34203 (Accessed: 8 October, 2016)

([25]) https://twitter.com/nark80ka/status/717349201726857216 (Accessed: 8 October, 2016)

([26]) Vendors of new psychoactive substances typically used the term 'pellets' rather than 'tablets' to describe such dosage forms as an apparent attempt to avoid scrutiny by regulatory agencies, including medicine regulatory agencies.

Seizures and collected samples reported to the EMCDDA and Europol have confirmed the presence of acryloylfentanyl in powders, liquids (often as nasal sprays), and tablets.

Similar to other fentanils, acryloylfentanyl may be diluted with sugars (dextrose, glucose, inositol, lactose, mannitol, or sucrose), and common cutting agents ([27]). Some of the powder seizures reported by Estonia (Section C) were reported to contain 'sugars'; no further details are available of these samples. A seizure of powder in a capsule reported by Denmark was reported to contain 'no lactose or other dilution agents' (EMCDDA & Europol, 2016; Breindahl et al., 2016).

The nasal spray solutions sold on the internet in Sweden claim to contain 20 mg acryloylfentanyl per 10 ml solution ([28]); quantification of acryloylfentanyl in nasal sprays in samples obtained from the Swedish drug market have found 20 mg (Helander, personal communication, October 2016).

Latvia reported 3 small seizures of acryloylfentanyl that also contained carfentanil and heroin (no quantification of the substances were reported).

Physical description

Melting point: hydrochloride (HCl) salt: 259–260°C (Zhu et al., 1981); 252–258°C with decomposition (Maryanoff et al., 1982); 191–194 °C (Essawi, 1999); free amine: 101–103 °C (Essawi, 1999).

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

Relevant data for fentanyl: at ambient temperature, fentanyl base is poorly soluble in water (0.032 mg per ml at pH = 5.9) (Prodduturi et al., 2009) yet intravenous injection of one millilitre of such a solution may have some psychoactivity (see Gorodetzky and Martin, 1965). The solubility of the citrate salt of fentanyl in water is ~25 mg/ml; in ethanol it is 7.1 mg/ml (Moffat et al., 2011).

([27]) Early studies reported that the concentrations of some extremely potent 'designer fentanils' in 'China White' powders did not typically exceed 1% (Henderson et al., 1990; Henderson, 1991). It was also found that the fentanils were uniformly distributed within a single sample but their concentration varied up to 300-fold between samples; the accidental overdose was thus attributed to the large intersample variability rather than to the 'clumping' of the drug within a sample (Henderson et al., 1990).

([28]) https://www.flashback.org/t2671134937 (Accessed: 8 October 2016)

Though no experimental data are available, acryloylfentanyl, being a close structural analogue of fentanyl, is highly lipophilic as indicated by their comparable calculated LogP values ([29,30]).

Chemical stability and typical reactions

Due to its high lipophilicity, carry-over of traces of acryloylfentanyl during sample handling and analysis can be problematic (see Degg, 2014).

Analytical profile

The ultraviolet and visible spectrum of acryloylfentanyl has not been reported.

Fourier Transform Infrared spectrum of the HCl salt ([31]) *(diamond ATR attachment)*

407, 444, 469, 507, 545, 604, 640, 677, 706, 742, 793, 954, 974, 982, 1031, 1046, 1089, 1141, 1164, 1266, 1317, 1340, 1366, 1388, 1411, 1452, 1479, 1494, 1593, 1614, 1649, 2403, 2453, 2936 and 3045 cm^{-1} (Slovenian National Forensic Laboratory, 2016; see also Breindahl et al., 2016)

Fourier Transform Infrared spectrum of the base form

675, 704, 747, 797, 967, 984, 1028, 1067, 1073, 1121, 1136, 1242, 1262, 1309, 1325, 1354, 1376, 1410,1452, 1495, 1594, 1618, 1654, 2767, 2805, 2948, 3028 and 3061 cm^{-1} (Slovenian National Forensic Laboratory, 2016)

Nuclear magnetic resonance (NMR) spectra

^{1}H-NMR in CD_3OD (400 MHz): δ 1.86 (qd, J = 8, 4 Hz, C*H*$_2$), 2.19–2.26 (m, 2H, C*H*$_2$), 3.05–3.10 (m, 2H, PhC*H*$_2$), 3.22–3.29 (m, 2H, C*H*$_2$), 3.33–3.37 (m, 2H, NC*H*$_2$),[#] 3.78 (m, 2H, C*H*$_2$), 4.90 (tt, J = 12, 4 Hz, 1H, N-C*H*),[#] 5.59 (dd, J = 10.5, 2 Hz, 1H, -CH=C*H'*), 5.91 (dd, J = 17, 10.5 Hz, 1H, CH_2=C*H*), 6.31 (dd, J = 17, 2 Hz, 1H, -CH=C*H*), 7.27–7.39 (m, 7H, Ph), 7.52–7.60 (m, 3H; Ph), 12.75 (bs, N^+) (Breindahl et al., 2016; see also Essawi, 1999; Slovenian National Forensic Laboratory, 2106). [#]Overlapping with signal from the NMR solvent.

^{13}C-NMR in DMSO (125 MHz): δ 27.6, 29.9, 50.0, 51.3, 56.9, 127.2, 128.1, 129.1, 129.1, 129.2, 129.5, 130.0, 130.9, 137.6, 137.9 and 164.7 (Slovenian National Forensic Laboratory, 2106; see also Breindahl et al., 2016).

([29]) LogP is logarithmic measure of the lipophilicity of a compound by its partition coefficient between an apolar solvent (usually 1-octanol) and an aqueous buffer.

([30]) The respective calculated LogP values for acryloylfentanyl and fentanyl are 4.13 and 3.89 (*ACD/ChemSketch* 2015 release version, Advanced Chemistry Development Inc., Toronto, Canada). The respective LogP values calculated by *StarDrop* version 6.3.1 software (Optibrium Ltd, Cambridge, UK) for acryloylfentanyl and fentanyl are 3.61 and 3.89. The measured LogP value for fentanyl is 4.05 (Hansch et al., 1995).

([31]) Spectrum was taken of the crude sample as received.

DEPT and two-dimensional (COSY and HSQC) NMR spectra are also available (Breindahl et al., 2016).

Chromatographic analyses coupled with mass spectrometry (GC-MS)

Electron impact (EI) mass spectrum of acryloylfentanyl (characteristic fragments): *m/z* 243 (base peak), 200, 189, 146, 105 and 55 (Breindahl et al., 2016; see also Essawi, 1999; Slovenian National Forensic Laboratory, 2106).

Quadrupole time-of-flight (QTOF) and matrix-assisted laser desorption/ionization Orbitrap (MALDI/Orbitrap) mass spectrometric analyses of acryloylfentanyl have also been described (Breindahl et al., 2016).

A highly sensitive capillary electrophoresis-electrospray-tandem mass spectrometry method recently developed for the trace level analysis of fentanils (Rittgen et al., 2012) could be applicable for acryloylfentanyl.

Immunoassay

Similar to fentanyl, it is expected that acryloylfentanyl does not give a positive response to immunoassay tests developed for morphine-type opioids. There is no data on whether immunoassays developed for fentanyl or other fentanils would give positive responses to acryloylfentanyl. Acryloylfentanyl did not show cross-reactivity with the immunoassay panel ABC-multi-10 (Simoco Diagnostic, Hillerød, Denmark), which includes MDMA (Breindahl et al., 2016) ([32]).

Presumptive colour tests

There is no information on the reaction of acryloylfentanyl to presumptive colour tests.

Methods and chemical precursors used for the manufacture

Information on the chemical precursors and the synthetic methods employed for acryloylfentanyl detected on the drug market within the European Union is limited to information from one seizure (discussed below).

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

([32]) Breindahl et al. (2016) mention that the initial tests carried out at a psychiatric ward at a Danish hospital with a sample of the unpurified powder indicated positive reaction for MDMA, therefore the sample was forwarded to further analysis, which then showed that the powder contained acryloylfentanyl and triethylamine. It is not known, however, that triethylamine would crossreact with an MDMA immunoassay or not.

Synthesis

The manufacture of acryloylfentanyl relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl. Accordingly, methods developed for the multistep synthesis of fentanyl are applicable to acryloylfentanyl but use a different acylating agent in the final acylation step.

Due to the therapeutic importance of fentanyl, several routes have been developed for its synthesis (see, for example, Zee et al., 1980; Casy and Huckstep, 1988; Gupta et al., 2005). These methods have been critically reviewed (Soine, 1986; Carroll and Brine, 1989; Hsu and Banks, 1992; Fritschi and Klein, 1995; Yadav et al., 2010; Vardanyan and Hruby, 2014). Most of these synthetic procedures are straightforward, use common laboratory equipment and precursors, and detailed recipes are available on the Internet ([33]).

While only basic knowledge of synthetic chemistry is required, due to the high potency of fentanils there is a serious risk of severe poisoning following accidental exposure during its manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substance ([34]). Likewise, accidental exposure to fentanils — such as skin contact, inhalation, or ingestion — pose a serious risk of poisoning to the public, law enforcement, emergency personnel, as well as medical and forensic laboratory personnel. In addition to exercising extreme caution when handling materials suspected to contain fentanils, working environments and personnel should be equipped with appropriate protective equipment. In addition, the antidote naloxone should be readily available to personnel in sufficient quantities; training in resuscitation and naloxone administration should also be available (CDC, 2017; CDC, 2013; DEA, 2016).

The two published synthetic methods of acryloylfentanyl describe the acylation of the common precursor 4-ANPP ([35,36]) with acryloyl chloride ([37]) (Zhu et al., 1981; Maryanoff et al., 1982) or 3-chloropropionyl chloride ([38]) (Essawi, 1998, 1999) as depicted in Figure 2.

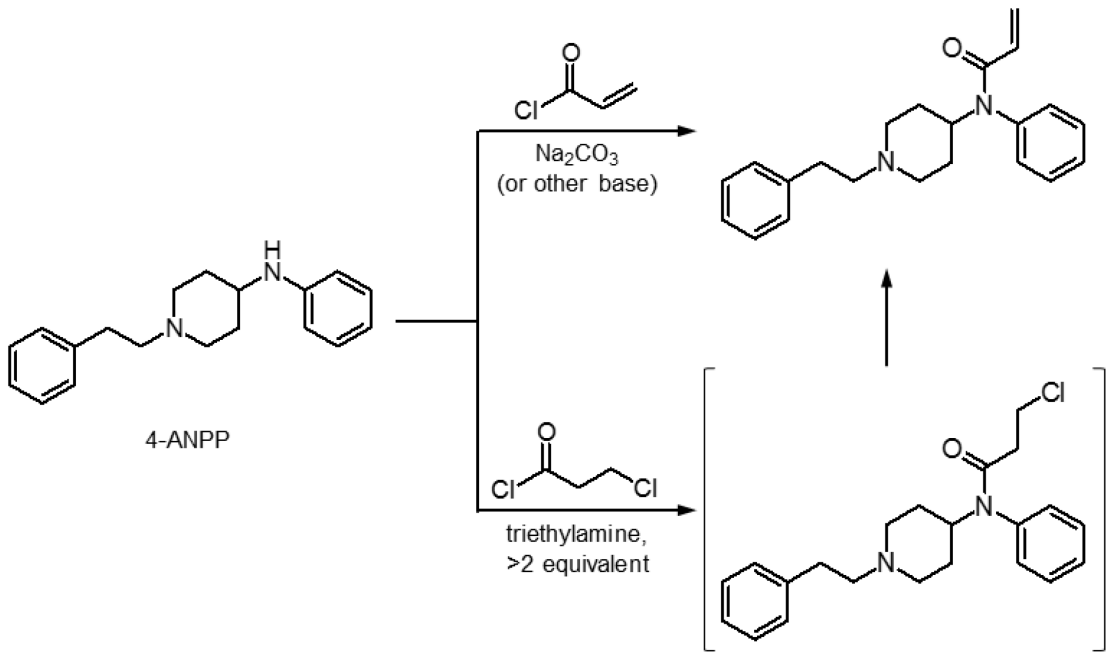
([33]) The detailed description of the most common procedure, often called the 'Siegfried method', is readily available on the Internet (see, for example, http://opioids.com/fentanyl/synthesis.html).

([34]) Self-educated clandestine chemists commented on the risk while discussing the synthesis of fentanyl and its potent 3-methyl and -methyl homologues (verbatim, all in bold!). "A synthesis as dangerous as this one should not be written in a way that novices think it is a very easy drug to synthesize cheaply, and earn a great money on. The truth is that the odds are AGAINST them with a potent opioid like this – a lot of them trying WILL get hurt, or in the best case scenario completely fails the reaction so that they doesn't ingest highly potent respiratory depressant, probably a lethal lose is present in the fume hood the reaction is taking place in, or dispersed into the room if the hood is dysfunctional or non-existant." (comment was posted on 7 May, 2002); available at: https://the-hive.archive.erowid.org/forum/showflat.pl?Cat=&Number=260275 (Accessed: 6 October 2016)

([35]) CAS RN: 21409-26-7. For analytical characterisation, see http://www.swgdrug.org/Monographs/4ANPP.pdf. Note that 1-(2-phenylethyl)piperidin-4-one, or NPP (CAS RN: 39742-60-4), a precursor to 4-ANPP, is also used for the manufacture of the bronchodilatory medicine fenspiride.

([36]) The synthesis of 4-ANPP from phenethylamine and ethyl (or methyl) acrylate is well documented (Beckett et al., 1959; Jończyk et al., 1978; Maryanoff et al., 1982). For another route, see Valdez et al. (2014).

Figure 2. Synthesis of acryloylfentanyl from *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) and acryloyl chloride (Zhu et al., 1981) (top) or 3-chloropropionyl chloride (Essawi, 1998, 1999) (bottom; the intermediate 3-chloropropionamide shown in brackets is not isolated).



Acylation of 4-ANPP with acryloyl chloride in the presence of a base, such as sodium carbonate, in an inert solvent affords directly acryloylfentanyl (top of Figure 2). In the similar synthesis of the acroyl analogue of the analgesic 2,5-dimethylfentanyl (phenaridine, also spelled as fenaridin) a 1.5 molar equivalent triethylamine was used (Vartanyan et al., 1989). The use of an additional base is, however, not necessary since the basic piperidine moiety present in the substance may serve as an acid scavenger.

Alternatively, acylation with 3-chloropropionyl chloride in the presence of an excess of a base, such as triethylamine, results in the simultaneous elimination of hydrochloride to provide the desired acryloyl product (bottom of Figure 2). This method has been used for the synthesis of another series of acryloyl fentanyl analogues (Girón et al., 2002).

A powder sample in a capsule seized in Denmark was shown to consist of mainly acryloylfentanyl and a substantial amount of triethylamine hydrochloride (27%) which indicates the use of triethylamine base as an acid scavenger during manufacture of the drug. In addition to triethylamine, 4-ANPP was also detected as a minor contaminant in the sample but no quantification was made (EMCDDA & Europol, 2016; Breindahl et al., 2016).

([37]) IUPAC name: prop-2-enoyl chloride; CAS RN: 814-68-6; European Community (EC) Number: 212-399-0.

([38]) IUPAP Name: 3-chloropropanoyl chloride, CAS RN: 625-36-5; European Community (EC) Number: 210-890-4.

Other acylation methods that use an activated ester of acrylic acid can also be used.

An alternative, potential synthetic route for the manufacture of acryloylfentanyl would involve the alkylation of *N*-phenyl-*N*-(piperidin-4-yl)acrylamide ([39]) with a phenethyl halide in the presence of sodium (bi)carbonate or another base ([40]).

None of the synthetic precursors mentioned above are included in Table I or Table II of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988. However, a proposal in June 2010, the USA Drug Enforcement Administration placed 4-ANPP (named ANPP in the regulation) into Schedule II of the Controlled Substances Act (DoJ-DEA, 2010).

It should be mentioned that, at least in theory, acryloylfentanyl may serve as a precursor to the internationally controlled fentanyl by saturating the double bond of the acrylamide moiety using catalytic hydrogenation (for a similar example, see Huckle et al., 1972).

In summary, the synthesis of acryloylfentanyl has been described in the literature. Other routes developed for the production of fentanyl may also be used for the manufacture of acryloylfentanyl. Information on the method(s) used for the production of acryloylfentanyl available on the drug market is limited to the detection of 4-ANPP and triethylamine hydrochloride that were detected in one seizure (EMCDDA & Europol, 2016; Breindahl et al., 2016).

Typical impurities encountered in seized and collected samples

Data on the impurities encountered in samples containing acryloylfentanyl is limited to the first seizure reported to the EMCDDA. In this seizure, 4-ANPP and triethylamine hydrochloride, believed to be used in the synthesis of acryloylfentanyl, were detected (EMCDDA & Europol, 2016; Breindahl et al., 2016).

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA have noted that acryloylfentanyl has typically been detected in powders, liquids or in tablets. Typically the liquids have been seized as unlabelled ready-to-use nasal sprays. In one case a capsule was seized that contained a powder (Section C) (EMCDDA & Europol, 2016; Breindahl et al., 2016).

([39]) Systematic name: *N*-phenyl-*N*-(piperidin-4-yl)prop-2-enamide.
([40]) This method was described for fentanyl and a series of its analogues (Janssen, 1965; reviewed by Hsu, 1992).

A1.3. Route of administration and dosage

Acryloylfentanyl can be administered orally as a powder (including in capsules), as tablets, or as a solution; it can also be administered intranasally or sublingually via a spray; inhaled by vaporising e-liquid solutions ('vaping'); inhaled by smoking or vaporising the 'free base'; injected; and, applied transdermally.

Data reported to the EMCDDA regarding acute intoxications suspected to involve acryloylfentanyl (Section D1.2) shows that intranasal administration, presumably using a nasal spray, was the most common route of administration (59%; 10 out of 17 non-fatal intoxications for which a route of administration was reported); while the most common physical form used were 'nasal solutions' (68%; 13 out of 19 cases for which a physical form was reported). Less commonly, snorting of powder or crushed tablets, oral consumption of tablets, and injection of a 'nasal solution' were also reported.

In one of the seizures reported to the EMCDDA acryloylfentanyl was detected in a liquid recovered from inside a syringe.

Discussions on user websites include the descriptions of homemade preparations for vaping acryloylfentanyl in an e-cigarette ([41]). In one case, a user describes the preparation of a 'homemade, rum-flavoured e-liquid prepared from 65% PG [propylene glycol] and 35% VG [vegetable glycerol]' to provide an 'acrylfent' solution of 24 mg/ml for vaping. In addition, an experience with a homemade transdermal patch preparation has also been discussed ([42])

Dosage and dosage regimens

Limited information is available regarding the dose and the dose regimens of acryloylfentanyl. 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. Given the difficulties of collecting such data accurately the information below should be used with caution.

Data reported to the EMCDDA regarding acute intoxications suspected to involve acryloylfentanyl indicate that a range of doses may be used, with re-dosing during the course of a day reported in some cases. This includes two cases that reported using '20 mg' intranasally per day and who appeared to have tolerance to the substance following use over the preceding months.

([41]) https://www.reddit.com/r/researchchemicals/comments/4y4imi/acrylfentanyl_observations_and_data

([42]) https://www.reddit.com/r/researchchemicals/comments/5osuzb/dmso_using_it_to_get_drugs_into_your_system/

Analysis of the concentration of acryloylfentanyl in nasal spray solutions from Sweden suggests that a 10 mL spray bottle typically contains 20 mg of the substance (Helander, personal communication, October 2016).

It should be noted that the preparation of solutions containing milligram amounts of substance is inherently prone to risks in weighing and dilution and therefore solutions with higher (or lower) concentrations can be mistakenly prepared and/or sold.

Some additional information on dosage is provided on user websites. As already highlighted, the assessment of such reports is problematic because the purity, amount and/or composition of the substance ingested are typically not known by the user. Moreover, the actual composition of the substance may differ over time and different geographical areas. The difficulty in assessing a 'typical' acryloylfentanyl dose from such websites is further compounded by the fact that miligrams and micrograms are sometimes used interchangeably.

For nasal sprays, doses of 0.0027 mg to 0.2 mg were reported on user websites. Some of these reports ([43]) suggested that oral doses of 5–12.5 μg of acryloylfentanyl may produce 'light' effects, and doses of 25–47.5 μg may produce 'strong' effects. The source of these figures is unknown.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacodynamics

In vitro studies

There has been one study published in the scientific literature on the opioid receptor binding of acryloylfentanyl. Maryanoff et al. (1982) determined the binding affinities of a series of compounds, including acryloylfentanyl, designed as potential covalent receptor affinity labels using a rat brain preparation and tritiated naloxone or naltrexone as competing opioid receptor ligands ([44]). Morphine, fentanyl and the highly potent fentanyl analogue (+)-3-methylfentanyl were used as comparative standards.

As seen in Table 1, the IC_{50} values ([45]) obtained for fentanyl and acryloylfentanyl were similar; morphine was somewhat less effective in inhibiting the binding of radiolabeled receptor antagonists.

([43]) http://drugs.tripsit.me/acryl-fentanyl#basic

([44]) Naloxone and naltrexone are potent antagonists (though may behave as inverse agonists also) of opioid receptors. Both have preference for μ opioid receptors, which are implicated in analgesia and withdrawal, as well as in respiratory depression and lethality in overdose cases.

([45]) The binding constant IC_{50} (half maximal inhibitory concentration) refers to the molar concentration of a drug that displaces 50% of a well-characterised ligand from the receptor preparation *in vitro*.

Table 1. Opioid receptor binding data for acryloylfentanyl, morphine, fentanyl and (+)-3-methylfentanyl (Maryanoff et al. 1982). The receptor affinity is expressed by IC_{50} values representing the concentration required for displacement of 50% of tritiated naloxone or naltrexone radioligands in a competition assay using rat brain homogenates.

Compound	**IC_{50} (nM) [^{3}H]naloxone**	**IC_{50} [^{3}H]naltrexone**
Morphine	4.2	27
Fentanyl	1.6	25
Acryloylfentanyl	1.4	17
(+)-3-methylfentanyl	0.6	1.3

The results of this study indicate that the opioid receptor affinity of acryloylfentanyl is similar to that of fentanyl and somewhat higher than that of morphine, at least in this particular rat brain preparation. Laboratory experiments failed to find evidence for irreversible binding of acryloylfentanyl to opioid receptors (Section D1.1).

A search in the PubChem Substance database for biological activity of acryloylfentanyl ([46]) identified 28 test results deposited, yet the substance was found inactive in all assays that included a range of non-opioid related targets (NCBI PubChem, 2012).

Animal studies

There have been two studies investigating the antinociceptive activity of acryloylfentanyl in the mouse (Zhu et al., 1981; Essawi, 1998, 1999).

The first publication mentioning acryloylfentanyl describes an extensive structure–activity relationship study involving 22 fentanyl analogues, with morphine and fentanyl as comparative standards (Zhu et al., 1981). The antinociceptive activities of morphine, fentanyl and acryloylfentanyl in mice upon intraperitoneal administration are shown in Table 2.

([46]) Available at: https://pubchem.ncbi.nlm.nih.gov/substance/144091883 (accessed: 6 October 2016).

Table 2. Antinociceptive activity of morphine, fentanyl and acryloylfentanyl in mice upon intraperitoneal administration (Zhu et al., 1981). The antinociceptive activity was assessed by the hot-plate test (55°C) measuring the latency of nociception.

Compound	**ED_{50} () (mg/kg)**	**Potency ratio to morphine**	**Potency ratio to fentanyl**
Morphine	13.9	1	0.0045
Fentanyl	0.062	224	1
Acryloylfentanyl	0.082	169.5	0.76

As Table 2 indicates, in this mouse model of analgesia, acryloylfentanyl is about 170-times more potent as an antinociceptive agent than morphine, though somewhat less potent than fentanyl.

Essawi studied five fentanyl analogues, including acryloylfentanyl, as potential receptor affinity labels and antinociceptive agents in the mouse using the hot-plate assay; morphine and fentanyl were used as comparative standards (Essawi, 1998, 1999) ([47]). Upon intraperitoneal administration at doses below 1 mg/kg, acryloylfentanyl was a more potent antinociceptive agent than fentanyl. While the effect of fentanyl at 0.1, 0.2 and 0.5 mg/kg dropped considerably at 60–70 minutes and became insignificant at 90–100 minutes after treatment, it was reported that at comparable doses, acryloylfentanyl maintained considerable analgesia at 90 and 120 minutes after administration. In its duration of action, the time-response profile of acryloylfentanyl resembled more closely that of morphine (20 mg/kg) than that of fentanyl. Remarkably, at 6.8 mg/kg and 17 mg/kg doses the antinociceptive effect of acryloylfentanyl was sustained up to 4.5 hours without signs of opioid toxicity. At the 25 mg/kg dose, it was reported that the motor activity was inhibited, but that the animals were not cataleptic and they returned to continuous circling behaviour 3.5 hours after treatment. However, following administration of a dose of 50 mg/kg, convulsions developed after 1 hour and 60% lethality was observed from apparent respiratory depression.

([47]) Fentanyl citrate, morphine sulfate were dissolved in water while aqueous solutions of the fentanyl analogues were prepared from the free base in the presence of equimolar citric acid. Appropriate doses of all test substance solutions were injected intraperitoneally at 10 ml/kg.

Pre-administration by 30 minutes of 2 mg/kg naloxone blocked the antinociceptive effect of 0.85 mg/kg acryloylfentanyl for about 40 minutes, after which this antagonist effect disappeared and analgesia and other morphine-like effects could be noted for about 50 minutes. A similar transient antagonist effect was observed when naloxone (2 mg/kg) was administered 40 minutes after acryloylfentanyl treatment (0.85 mg/kg): the reversal of the antinociceptive effect lasted for 70 minutes, and then antinociception returned to the same level as before naloxone administration. The author of the study concluded that acryloylfentanyl 'has a mode of interaction with μ □receptors different from morphine' ([48]).

In summary:

- Studies *in vitro* and in mice establish acryloylfentanyl as a potent and long-lasting antinociceptive agent acting on the opioid system.
- The antinociceptive activity of acryloylfentanyl is blocked by the opioid antagonist naloxone though this protective effect is transient.
- The acute toxicity of acryloylfentanyl has not been determined but based on observations during a mouse-study, it appears to be similar to that of fentanyl.

Pharmacokinetics

Due to its lipophilicity (Section A.1.1.), acryloylfentanyl, like fentanyl, is expected to readily cross the blood–brain barrier and also diffuse into fat and other tissues, i.e., it is likely to have a large volume of distribution.

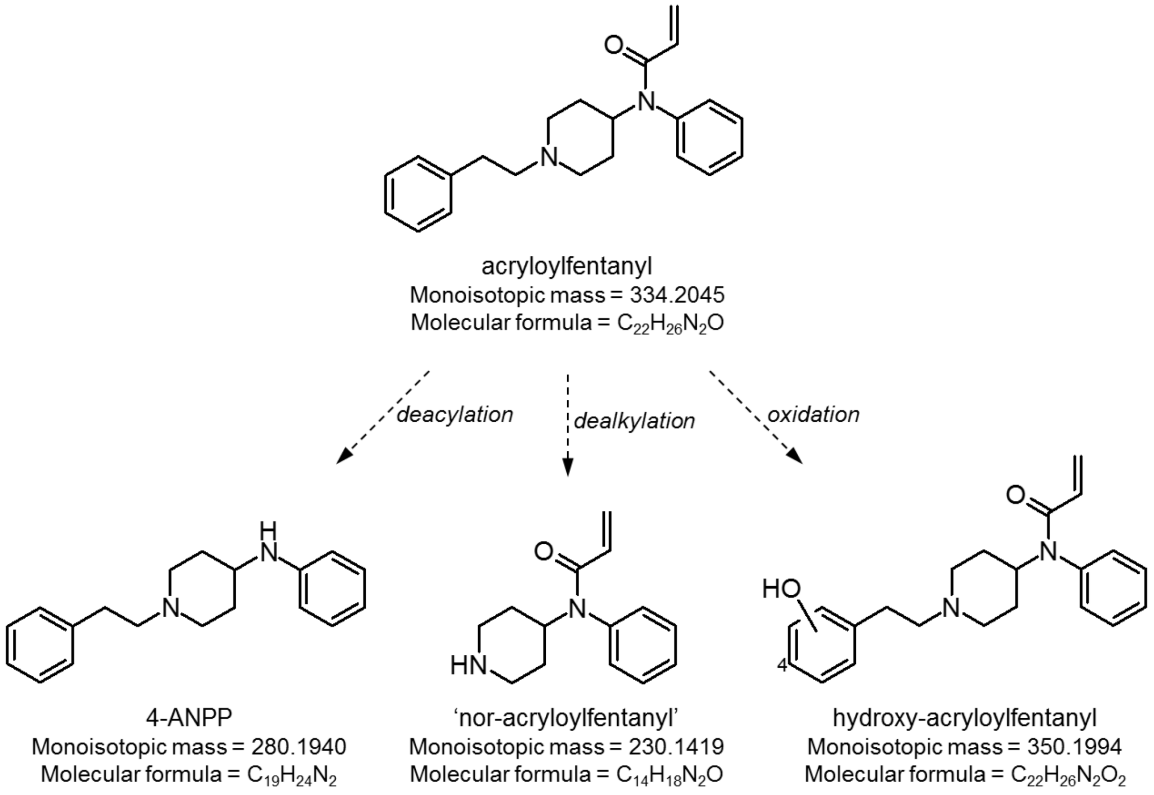
There appears to be no preclinical or human clinical study on the pharmacokinetics, including metabolism, of acryloylfentanyl. Nevertheless, the pharmacokinetics and the metabolic pathway of acryloylfentanyl are expected to be similar to that of fentanyl (McClain et al., 1980; Goromaru et al., 1984; Guitton et al., 1997; DePriest et al., 2015) or acetylfentanyl (Patton et al., 2014; Melent'tev et al., 2015; Poklis et al., 2015).

([48]) The proposal by Essawi (Essawi, 1999) that the observed temporary antidotal effect of naloxone was due to noncompetitive binding of the morphine analogue naloxone to an allosterical site whereby inhibiting the pharmacological response of covalently bound arcyloylfentanyl until naloxone was eliminated appears to be in conflict with earlier research indicating the lack of covalent binding of acryloylfentanyl to opioid receptors *in vitro* (Maryanoff et al., 1982). A possible explanation for the discrepancy could be that Essawi carried out the mouse experiments *in vivo* while Maryanoff et al. (1982) used rat brain receptor preparations *in vitro*.

The primary route in fentanyl metabolism is oxidative *N*-dealkylation which is catalysed by cytochrome P450 (CYP450) enzymes and leads to the biologically inactive desphenethyl metabolite of fentanyl, usually called 'norfentanyl' ([49]) (Labroo et al., 1997; see also Goromaru et al., 1984; Higashikawa and Suzuki, 2008a).

It is expected that one of the main metabolites present in biological matrices is the 'desphenethyl' derivative of acryloylfentanyl, that is 'acryloyl norfentanyl' ([50]). Amide hydrolysis (deacylation) is a minor pathway for fentanyl and probably an insignificant biotransformation for the acryloyl analogue. Terminal hydroxylation of the acyl chain, which is also a minor biotransformation step for fentanyl in humans, produces what is often called 'hydroxyfentanyl' ([51]) but such a hydroxylation cannot take place in case of acryloylfentanyl.

Figure 3. Some potential human metabolites of acryloylfentanyl. Note that due to incomplete acylation during manufacture, 4-ANPP could be present in the consumed products thus its detection in biological matrices might not be indicative of metabolism.



([49]) Systematic name: *N*-phenyl-*N*-(piperidin-4-yl)propanamide. Molecular weight: 232.32.
([50]) Systematic name: *N*-phenyl-*N*-(piperidin-4-yl)prop-2-enamide. Molecular weight: 230.30.
([51]) Systematic name of this metabolite: 3-hydroxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide.

There is some information on the biological activity of two potential metabolites of acryloylfentanyl. An study assessing the opioid-like activity of several fentanyl metabolites in the guinea pig ileum assay, found that 4-ANPP and 4-anilinopiperidine ([52]) were less potent than fentanyl by 4 to 5 orders of magnitude (Schneider and Brune, 1986). Compared to morphine, these two anilines were also less potent by 3 to 4 orders of magnitude. The only metabolite showing significant activity in this study was a phenolic derivative hydroxylated at the 4-position of the phenylethyl moiety of fentanyl ([53]) (Figure 3), the activity of which was found to lie between morphine and pethidine. This implies that the corresponding phenolic metabolite of acryloylfentanyl ([54]), if formed, may have some level of opioid activity and thus may contribute to the biological, including toxicological, properties of the parent substance.

No information was found in the published literature regarding two other potential metabolites of acryloylfentanyl: i) the desphenethyl derivative of acryloylfentanyl and ii) nor-acryloylfentanyl ([55]).

Inter-individual genetic variability in metabolising enzymes

For fentanyl, oxidative dealkylation by hepatic CYP450 3A4 and by CYP450 3A5 isoenzymes has been demonstrated (Labroo et al., 1997; Jin et al., 2005; see also Guitton et al., 1997). The wide variation of the expression of the genes coding for these CYP450 3A isoenzymes among populations is of clinical significance, but the toxicological consequence of such polymorphisms has not been investigated in fentanyl poisonings.

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

Should acryloylfentanyl undergo oxidative dealkylation by hepatic CYP450 3A4 and by CYP450 3A5 isoenzymes then the use of this substance with inhibitors of these isoenzymes, such as ketoconazole, clarithromycin, indinavir, itraconazole, nefazodone, ritonavir, saquinavir (all strong CYP3A inhibitors), erythromycin, fluconazole, grapefruit juice, verapamil (all moderate CYP3A inhibitors) (EMA, 2016; EMA, 2017; McCance-Katz, et al., 2010) may result in increased plasma concentration of acryloylfentanyl which could be toxicologically significant. Overall, this could increase the risk of poisoning including potentially fatal respiratory depression.

([52]) Systematic name: *N*-phenylpiperidine-4-amine.
([53]) Of the potential mono- and dihydroxylated metabolites only this substance, that is *N*-{1-[2-(4-hydroxyphenyl)ethyl]piperidin-4-yl}-*N*-phenylpropionamide, was tested.
([54]) Systematic name: *N*-{1-[2-(4-hydroxyphenyl)ethyl]piperidin-4-yl}-*N*-phenylprop-2-enamide
([55]) Exact structure search was done in *SciFinder*®.

The concomitant use of other central nervous system (CNS) depressants with opioid analgesics, including other opioids, sedatives/hypnotics (such as the benzodiazepines and the z-drugs), ethanol, gabapentinoids (pregabalin and gabapentin), tranquillisers, sedating anti-histamines, and skeletal muscle relaxants may produce additive depressant effects (EMA, 2016; EMA, 2017). Of note in this respect is that polydrug use was common in the deaths reported to the EMCDDA, including the use of other CNS depressants such as benzodiazepines, pregabalin, gabapentin and ethanol (Section D).

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 serotonin syndrome, a potentially life-threatening condition (EMA, 2016; EMA, 2017). 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 acryloylfentanyl.

Severe and unpredictable potentiation by MAOI inhibitors has been reported with opioid analgesics (EMA, 2016; EMA, 2017).

Similar to fentanyl, the use of partial opioid agonists/antagonists (such as buprenorphine, nalbuphine, pentazocine) which have high affinity to opioid receptors but relatively low intrinsic activity could partially antagonise the effects of acryloylfentanyl and may induce withdrawal symptoms in people who are opioid dependant (EMA, 2016; EMA, 2017).

Effects on ability to drive and operate machines

No studies of the effects of acryloylfentanyl 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 acryloylfentanyl.

A3. Psychological and behavioural effects

Information on the psychological and behavioural effects of acryloylfentanyl is limited to serious adverse events reported to the EMCDDA and self-reported experiences from user websites.

The psychoactivity of acryloylfentanyl is reportedly similar to that of other opioids and characterised by relaxation and euphoria. Internet forums rarely mention side or adverse effects typical of opioids.

For fentanyl, which is structurally very similar to acryloylfentanyl, as little as 0.025 to 0.050 mg doses given intravenously could produce psychoactive effects (or the 'high'), which are often compared to heroin. For example, an early study with "postnarcotic addicts" compared the miotic and euphorogenic effects of fentanyl and morphine, both administered intramuscularly (Gorodetzky and Martin, 1965): fentanyl at the 0.8 and 1.6 mg per 70 kg doses was 25 times as potent as morphine in constricting pupils but 50 times as potent as morphine as measured by opiate symptom scores as well as subject and observer 'liking' scores; the effects of fentanyl gradually diminished after the second hour. Morphine, on the other hand, did not show such a decrease in effects until after the fourth hour. Though human clinical studies are lacking, it may be assumed that the opiate-like effects of acryloylfentanyl manifest at doses similar to those observed for fentanyl. User self-reports posted on internet forums mention sub-milligram doses administered by nasal spray as being psychoactive.

A4. Legitimate uses of the product

Acryloylfentanyl is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. Analytical reference materials are available commercially. There is currently no information that suggests acryloylfentanyl may be used for other legitimate purposes.

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

There is no marketing authorisation (existing, ongoing or suspended) for acryloylfentanyl 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 and Europol, 2016).

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

B2. Human data

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

The limited information available from user websites suggests that some users of acryloylfentanyl report an urge to re-dose as well as symptoms suggestive of withdrawal.

While no specific data exists for acryloylfentanyl, it is well established that opioid analgesics such as fentanyl have an abuse liability and can induce tolerance and dependence. Research will be required in order to determine such effects.

Section C. Prevalence of use

Information from seizures, collected and biological samples

Acryloylfentanyl was formally notified on 7 July 2016 by the EMCDDA on behalf of the Danish National Focal Point, in accordance with Article 4 of the Council Decision. The Reporting Form details a capsule that was seized on 11 May 2016 by the Department of Forensic Psychiatry of the Aalborg Psychiatric Hospital. The identification and analytical characterisation was based on a range of analytical techniques GC-MS, high-resolution mass spectrometry (HR-MS) and NMR. The GC-MS analysis showed that the synthetic precursor used was 4-ANPP, which can also be used for the synthesis of fentanyl. The impurities, triethylamine hydrochloride and 4-ANPP were detected (Section A1.1) (EMCDDA & Europol, 2016; Breindahl et al., 2016).

Since then, a total of 6 Member States have reported detections of acryloylfentanyl ([56]) (EMCDDA and Europol, 2016).

Information from seizures

A total of 5 Member States (Denmark, Estonia, Finland, Latvia and Sweden) reported seizures ([57]) of acryloylfentanyl to the EMCDDA and/or Europol.

([56]) '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.)

([57]) Many 'seizures' relate to individual case-level data, however, some data provided to the EMCDDA are aggregated at the country level. Data is drawn from the Joint Report Questionnaires and data provided in the bi-annual data gathering (EU EWS progress and final reports) and from individual Reporting forms submitted on an ad hoc basis.

Information reported to the EMCDDA and Europol indicates that 162 seizures of acryloylfentanyl have been reported by: Denmark (1 seizure), Estonia (61), Finland (1), Latvia (17), and Sweden (82). All the seizures were made during 2016 and 2017 by Police or Customs. Many seizures have been made at street-level.

These seizures included:

- 84 seizures of powder amounting to 112.667 grams (Estonia, Latvia and Sweden). In Latvia, one of the seizures was made at a scene of death ([58]); while an additional seizure was made in prison from incoming mail (a package with light beige powder which was hidden inside a tube for cosmetic cream). Latvia reported 3 small seizures of acryloylfentanyl that also contained carfentanil and heroin (no quantification of the substances were reported).

- 50 seizures of liquids, made in Sweden (49) and in Latvia (1), amounting to a total of 1495 mL;

- 27 seizures of tablets (Sweden and Finland) amounting to 896 tablets. This includes one seizure of 99 blue oval tablets with no logos or markings that was seized in Finland.

- 1 capsule seized in Denmark.

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

Information from collected samples

Slovenia reported a sample of light green powder which was purchased from an Internet vendor. The sample was shipped from China and was received in May 2016.

Information from biological samples

A total of 54 detections where acryloylfentanyl was analytically confirmed in biological samples were reported by three Member States: Denmark (1), Estonia (3), and Sweden (50).

These related to:

- 47 deaths reported by Denmark (1), Estonia (3), and Sweden (43).

([58]) Latvia reported 1 death where acryloylfentanyl was identified in seizure made at the scene of death. However, post-mortem analysis of biological samples only detected alcohol.

- 6 cases from Sweden related to patients undergoing drug treatment, persons suspected of having consumed drugs, or persons committing minor offences, or crimes.

- 1 case from Sweden of a person suspected of driving under the influence of drugs.

Availability, supply, price

Data from seizures, collected samples and acute intoxications suspected to involve acryloylfentanyl suggests that the substance is sold online, typically as a powder and as ready-to-use nasal sprays. Acryloylfentanyl is sold as a 'research chemical' online and is available in small and wholesale amounts. In addition, 3 small seizures of acryloylfentanyl that also contained carfentanil and heroin have been reported (no quantification of the substances were reported). Overall, the available information suggests that acryloylfentanyl is produced by chemical companies based in China. In February 2017 it was announced that acryloylfentanyl will be controlled in China as of the 1 March 2017. This control measure may deter at least the open manufacture and sale of this substance by such chemical companies and which are involved in the supply of the substance in Europe.

Availability from Internet vendors

A structured search by the EMCDDA of online vendors ([59]) of acryloylfentanyl on the surface web ([60]) was conducted in October 2016. The search identified 9 vendors that appeared to be based in, and/or claim to have a presence in China (n=6 sites), in Hong Kong (n=1), in India (n=1 sites) and in Denmark (n=1). Eight of the sites presented information in English and 1 site in Danish.

Three of the sites only provided prices for acryloylfentanyl on application, 2 presented prices as 'negotiable' and 1 website displayed no information on price. In the latter, quantities from 10 gram to 1000 kg were on sale, packaged in foil bags, drums or bottles. The remaining 3 sites listed quantities and prices. Briefly:

- acryloylfentanyl was typically sold as a 'research chemical';

([59]) This includes vendors that appear to be consumer-orientated as well as vendors, for example on B2B sites, which appear to be manufacturers and/or wholesalers. It excludes those selling acryloylfentanyl through online classified advertisements, social media, and user websites.

([60]) The search of online vendors of acryloylfentanyl was performed on 21/10/2016 using the search strings: 'buy acryloylfentanyl' (searches in English, Swedish and Danish, including variations in spelling). The first 100 results were recorded and the sites reviewed. Each identified vendor site was then scored for information on warehouse location, quantities and prices, and substance marketing.

- the minimum quantity offered was 25 tablets (n=1 sites) with a price of EUR 67 ([61]);
- the maximum quantity offered was 500 g (n=1 sites) with a price of EUR 7,322;
- 2 of the websites identified were part of the TOR routing system which suggests they were dark web marketplaces. In both sites acryloylfentanyl was offered as a powder and advertised as a 'research chemical';
- 1 website sold acryloylfentanyl as a nasal spray listed as 25 mg / 10 mL with a price of EUR 67.

In addition the 'Opiates' section of the darknet marketplace *Valhalla* contained at least one vendor who offered acryloylfentanyl hydrochloride: the respective prices for 100 g, 250 g and 500 g of substance were 672.37 EUR ([62]) 4464.29 EUR ([63]) and 7142.86 EUR ([64])

The precursors NPP and 4-ANPP which can be used to synthesize acryloylfentanyl are offered from gram to bulk (multi-kilogram) quantities on the Internet from dozens of suppliers. For the purposes of illustration, prices for the immediate precursor 4-ANPP range from USD 75 per 100 gram to USD 5000 per 1 kg.

Prevalence of use

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

According to information from Swedish Police on 807 buyers of the acryloylfentanyl, the substance is used mostly by men (80%) aged 21 to 41 years. No further details were provided.

A total of 3 small seizures of acryloylfentanyl that also contained carfentanil and heroin were reported by Latvia. The overall significance of these seizures is unclear; however, the identification of carfentanil is of serious concern given its potency. In addition, the identification of heroin in the seizures may suggest that acryloylfentanyl is being supplied through the illicit heroin/opioid market.

([61]) Prices listed in DKK were converted to EUR according to Google exchange rate from the 25.10.2016 (DKK 1 = EUR 0.13).
([62]) Available at: http://valhallaxmn3fydu.onion.rip/products/33602 (accessed: 8 October, 2016).
([63]) Available at: http://valhallaxmn3fydu.onion.rip/products/33603 (accessed: 8 October, 2016).
([64]) Available at: http://valhallaxmn3fydu.onion.rip/products/33604 (accessed: 8 October, 2016).

Section D. Health risks
D1. Acute health effects

D1.1. Animal data

Data on the acute toxicity of acryloylfentanyl is limited to a single study in mice. This study reported that intraperitoneal injection of 25 mg/kg of acryloylfentanyl caused a transient suppression of motor activity; while, at a dose of 50 mg/kg the drug produced convulsions 1 hour after drug administration and 60% lethality was observed from apparent respiratory depression (Essawi, 1998, 1999). From these data, an acute mouse LD_{50} value between 25 and 50 mg/kg upon intraperitoneal administration may be suggested. While no comparative standard was used in this particular study, data from other studies on fentanyl suggest that the acute toxicity of acryloylfentanyl is similar to that of fentanyl.

What is the toxicological relevance of the acrylamide moiety of acryloylfentanyl?

Expecting that the reactive acrylic moiety could irreversible modify even inactivate the opioid receptor protein by virtue of a conjugate addition ('Michael addition') of nucleophilic amino acid side chains, especially sulfhydryl groups of cysteines, in and around the fentanyl-binding pocket, acryloylfentanyl was one of the fentanyl analogues designed as potential, covalently binding affinity labels for the receptor (Maryanoff et al., 1982). Yet, in spite of having high affinity to opioid receptors (Table 2), acryloylfentanyl did not exhibit irreversible covalent binding *in vitro* ([65,66]).

Interestingly, the structurally related □- and □-chloroacryloyl analogues of fentanyl ([67]) while chemically reactive in solution ([68]) were weak opioid receptor ligands and failed to bind covalently to the receptor protein *in vitro* (respective IC_{50} values were 69 and 60 nM) (Archer et al., 1985). The sustained antinociceptive activity observed in a recent study (Essawi, 1999) is thus unlikely related to the 'reactivity' of the acrylamide moiety of acryloylfentanyl.

([65]) After incubation, acryloylfentanyl could completely be 'washed out' from the receptor preparation; the recovered receptor was then able to bind radiolabeled naltrexone indicating reversible binding of the drug.
([66]) Similar non-irreversible binding was observed for an acrylamide derivative of naltrexamine (Archer et al., 1985).
([67]) Respective alternative names: 2- and 3-chloropropenamide analogues of fentanyl.
([68]) As estimated by the rate of Michael addition of 4-methoxybenzenethiol to the chloroacryloyl species.

Although recent studies indicate that acrylamides may target sulfhydryl or hydroxy residues of proteins (LoPachin and Gavin, 2012; Jöst et al., 2014), the actual irreversible (covalent) binding of the acryloyl moiety seems to depend on the chemical reactivity of the acrylamide moiety on one hand and on the spatial orientation of the potentially reactive ligand at the binding site, in particular on the molecular microenvironment, that is on the presence and accessibility of sulfhydryl groups at the binding pocket, on the other (see, for example Archer et al., 1985) ([69])

The small molecule acrylamide (CH_2=CHCONH_2) has a wide range of industrial uses, especially in the manufacture of various polymers; it is also formed during high-temperature cooking thus may be present in food. Acrylamide has been shown to be a skin irritant, neurotoxic, mutagenic and is considered to be a probable carcinogen in humans (Xu et al., 2014) ([70]). There is, however, little information on the acute or chronic toxic properties of *N*-phenylacrylamide-related substances.

It must be noted that the polymerisation processes involving acrylamide or other acrylic type substances require photochemical or free radical initiation, thus spontaneous polymerization of acryloylfentantyl in the body can be ruled out. Whether any 'biochemical' initiator could be involved in the observed long-lasting activity *in vivo* (Section A.2) of acryloylfentanyl can only be speculated. It must also be noted that no stability studies have been carried out with acryloylfentanyl.

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of acryloylfentanyl and/or its metabolites in humans. However, the comparable pharmacology of acryloylfentanyl and fentanyl in preclinical studies suggests some toxicological similarity. For fentanyl the estimated human lethal dose could be as low as 2 mg when injected intravenously (Marquardt et al., 1995; see also Baselt, 2000; Reeves and Ginifer, 2002; Moffat et al., 2011).

Data from serious adverse events associated with acryloylfentanyl are discussed in Section D.1.2.2. Based on the data reported, the clinical features presented in cases of intoxication suspected to involve acryloylfentanyl appear to be similar to those found with fentanyl and other opioid analgesics. These include the opioid triad of miosis, unconsciousness, and respiratory depression; nausea and vomiting, dizziness were also reported.

([69]) While chloroacryloyl fentanyl analogues were reversible opioid receptor ligands, chloroacryloyl derivatives of naltrexamine bound irreversibly to the receptor protein (Archer et al., 1985).

([70]) For useful references, see: https://en.wikipedia.org/w/index.php?title=Acrylamide&oldid=742413264

Acute intoxications reported by the Member States

A total of 21 acute intoxications associated with acryloylfentanyl were reported by 1 country: Sweden ([71]). All 21 cases related to acute non-fatal intoxications that presented to hospital emergency departments between March and August 2016 and reported to the Swedish Poison Information Centre. All were classed as suspected cases as there was no analysis of biological samples or other samples used by the patients ([72]).

In all cases the patient either reported that they had used acryloylfentanyl and/or medical staff had other information to suggest that they had consumed acryloylfentanyl.

Demographics

Of the acute intoxications, 18 (86%) were male; 3 (14%) were female. The mean age of the male cases for which an age was known (n=7) was 35 years (median 29) and ranged from 22 to 44 years; for the female cases the ages were 22, 23, and 40 years.

Substances analytically identified in biological samples

None of the 21 cases were subject to analytical confirmation in biological samples.

In some cases, users reported taking other substances: 4-methylmethylphenidate, 3-hydroxyphenazepam, 4-chloro-PPP, *N*-ethylhexedrone, amphetamine, oxycodone, buprenorphine, ethanol and 4-chloro-PHP.

([71]) In addition, aggregated data regarding 7 non-fatal intoxications suspected to involve acryloylfentanyl occurring between March and September 2016 was also reported by the Swedish Poisons Information Centre. Acryloylfentanyl was not analytically confirmed in any of these cases. As this is aggregated data, no further details regarding the individual cases are known and it is therefore possible that some of these cases are duplicates of the 21 acute intoxications. These aggregated cases are not considered further in the analysis.

([72]) For the purposes of this report the following definitions are used. Confirmed case means that information on exposure to acryloylfentanyl is available from analytical confirmation in one or more biological samples taken from a patient. Probable case means that information on exposure was only available from the analytical confirmation of acryloylfentanyl in a drug sample and that there is a reasonable probability that the patient was exposed to that drug sample. Suspected case means that information on exposure is typically limited to the name of the substance that the patient believes that they have consumed and/or from packages containing the drugs that the patient is thought to have consumed. As a result, information on the features of the intoxication from probable and suspected cases should be interpreted with caution.

Seriousness of the intoxications

Data on the seriousness of the intoxication as classified by the poison centre were reported for all 21 cases:

- In 13 out of the 21 cases the seriousness of the intoxication was classified as life threatening and required treatment in hospital;
- In 8 out of the 21 cases the intoxication was classified as non-life threatening but required treatment in hospital.
- Information on the length of hospital stay was not available in the cases.

Clinical features

Data on clinical features/ symptoms related to the 21 acute intoxications included: miosis, unconsciousness, and respiratory depression; tachycardia, somnolence, restlessness, and nausea/vomiting were also reported. However, the lack of analytically confirmed drugs hinders the interpretation of this as other drugs may have caused or contributed to the symptoms observed. Nevertheless, such symptoms appear to be consistent with use of an opioid analgesic.

The use of the antidote naloxone was reported in 8 of the cases, with apparent reversal of the poisoning reported in 4 of these cases (patients 'woke up'). This is suggestive of poisoning with an opioid analgesic.

Route of administration and physical form of the substance/product

Data on the route of administration was available for 17 out of 21 cases. The substance was predominantly taken nasally (presumably as a nasal spray), snorted, or taken orally, with one case involving injection of a 'nasal solution'. The substance was typically consumed as a nasal solution, and to a lesser extent as a powder or tablets.

Acute intoxications identified from other sources

One paper was identified that reported that the Swedish STRIDA project has detected an unspecified number of confirmed acute intoxications associated with acryloylfentanyl. No further details were provided (Helander & Bäckberg, 2016).

Deaths reported by the Member States

A total of 47 analytically confirmed deaths associated with acryloylfentanyl were reported by three Member States: Denmark (1 case), Estonia (3), and Sweden (43).

No additional information is currently available for the deaths reported by Estonia. Therefore, the analysis below is restricted to the 44 deaths reported by Denmark and Sweden.

Demographics

Of the 44 deaths, 38 were male (86%) and 6 were female (14%). The mean age of the male decedents was 31 years (median 29) and ranged from 19 to 54 years; the mean age of the female decedents was 42 years (median 43) and ranged from 29 to 50 years.

Number of deaths by year

The deaths occurred between April and December 2016. More than 70% of the deaths (32) occurred between June and August 2016; with 10 deaths in June, 9 in July, and 13 in August.

Cause of death & toxicological significance

In at least 40 deaths, acryloylfentanyl was either the cause of death or is likely to have contributed to death (even in presence of other substances); in 2 of these deaths acryloylfentanyl was the sole drug present. Acryloylfentanyl was quantified in all cases. Post-mortem blood concentrations between 0.01 and 5.0 ng/g blood were recorded (mean 0.78; median: 0.19) (somewhat but not exactly equivalent to µg/L).

A range of other substances were found in the deaths, including: benzodiazepines, zopiclone, gabapentinoids (pregabalin and gabapentin), ethanol, cannabinoids (including synthetic cannabinoids), synthetic cathinones, amphetamines, antidepressants, antipsychotics. In 38 cases, acryloylfentanyl was the sole opioid present. In the remaining 6 cases, other opioids detected were buprenorphine (2 deaths), oxycodone (1); oxycodone and hydrocodone (1); oxycodone and 4-fluoro-isobutyrfentanyl (1); and, 4-chloro-isobutyrfentanyl (1).

Overall, whilst other substances may have contributed to some toxicity in their own right, a synergistic effect with acryloylfentanyl would have been likely (e.g. other CNS depressants such as ethanol, benzodiazepines, z-drugs, gabapentinoids, and opioids, etc.). Nevertheless, the pharmacological opioid nature of acryloylfentanyl means the primary toxic contribution could be attributed to the drug and death may not have occurred if acryloylfentanyl had not been used.

In all deaths there was a lack of information regarding any symptoms experienced by the deceased prior to death.

Circumstances of death

Information regarding the circumstances of death was reported for 43 out of 44 cases. In more than 70% of the cases (32), the individuals were found dead or died in a home environment (their own or someone else's); with 5 found dead in bed. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxications); however, in 3 cases the deceased was described as being unconscious prior to death, and in 1 of these cases it was reported that the deceased lost consciousness 10 minutes after using acryloylfentanyl. In a further case, the deceased was described as being found on the floor with a 'seizure disorder' and that attempts at resuscitation failed.

Deaths identified from other sources

No other deaths were identified from other sources.

D2. Chronic health effects

D2.1. Animal data

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

D2.2. Human data

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

D3. Factors affecting public health risks

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

Acryloylfentanyl is sold as a drug in its own right and offered for sale by internet retailers and for sale in both retail and wholesale quantities. It has been sold as a 'research chemical' in several physical forms, including as powders and ready-to-use nasal sprays.

Limited information from seizures of acryloylfentanyl suggests that acryloylfentanyl may have been sold on the illicit drug market, including the illicit opioid/heroin market.

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

There is limited information on user websites regarding the effects and adverse effects related to the use of acryloylfentanyl. The users appeared to be generally aware of the opioid-like (wanted and unwanted) effects of this substance.

Some discussions on these sites describe acryloylfentanyl as 'longer lasting' after dosing than other new synthetic opioids.

D3.3. Characteristics and behaviour of users

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

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

Information from the deaths reported to the EMCDDA highlights, that, besides acryloylfentanyl, other opioids were only detected in 6 of the 44 deaths (13.6%). This suggests that a majority of the decedents may have had no tolerance to opioids. In addition, the data also shows that polydrug use was common, including the use of other CNS depressants (Section D1.2).

D3.4. Nature and extent of health consequences

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

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

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

- the difficulty of diluting fentanils ([73]);
- the lack of experience of users with this new substance (in terms of a lack of familiarity with the effects and dose of the substance);
- the concomitant use of other CNS depressants (such as other opioids, benzodiazepines, gabapentanoids, and ethanol (alcohol));
- in some cases no apparent tolerance to opioids; and,
- the environment in which the substance is used — typically in the home environment.

The majority of the deceased were found dead at home, including a number that were found dead in bed. It is reasonable to assume that in at least some of these cases the poisoning with acroylfentanyl was so severe that they were unable to call for help.

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

Importantly, it is also reasonable to assume that the antidote naloxone will reverse poisoning (overdose) caused by exposure to acryloylfentanyl. However, larger than normal as well as repeated doses may be required to fully reverse poisoning due to the potency of the fentanils, their half-lives, and the dose used (CDC, 2013; FDA, 2016). Clinical and community experience in treating poisonings caused by exposure to fentanils supports this assertion (Klar et al., 2016; Sutter et al., 2017). Stocks and availability of the antidote naloxone, as well as adequacy of training in how to resuscitate poisoned patients may need to be assessed.

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

- Sufficient antidote stocking was an important factor as the supplies of naloxone at the hospital were quickly depleted because of the large number of patients that presented over a short period of time, as well as the need of some patients for several milligrams of naloxone as bolus dosing and prolonged infusion times.

- The hospital required emergency deliveries of naloxone to keep supplies sufficient for patient care.

- A notable clinical difference observed was not only that some patients required prolonged naloxone infusions but also the recurrence of respiratory depression in the hospital after 8 hours of observation without naloxone.

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

Adding to the challenges posed by the fentanils is evidence from Europe, the United States, and Canada that they are being sold to unsuspecting users in/as heroin, counterfeit medicines (including commonly used opioid analgesics and benzodiazepines), cocaine, and other illicit drugs ([74]). As users will be unaware of this, it increases the risk of severe and fatal poisoning in both opioid users and especially other groups who may have no existing tolerance to opioids (Klar et al., 2016; HCCCSF, 2016a; HCCCSF, 2016b; SFDPH, 2015; Tomassoni et al., 2017). Non-opioid users are unlikely neither to be aware of these risks nor to have access to community-based naloxone programmes, including take-home naloxone (EMCDDA, 2015; EMCDDA, 2016).

D3.5. Long-term consequences of use

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

([74]) In 3 seizures reported to the EMCDDA, acryloylfentanyl was detected with carfentanil and heroin. This may suggest that acryloylfentanyl is being sold on the illicit opioid market, including heroin market (Section C).

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

There is very limited data on the conditions which acryloylfentanyl is obtained and used. It appears acryloylfentanyl has been sold on the surface web and darknet marketplaces, typically as powders and ready-to-use nasal sprays.

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

In more than 70% of the deaths reported to the EMCDDA, the individuals were either found dead or died in a home environment (their own or someone else's).

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

Section E. Social Risks

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

E1. Individual social risks

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

E2. Possible effects on direct social environment

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

E3. Possible effects on society as a whole

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

As discussed above, accidental exposure of acryloylfentanyl and other fentanils — such as skin contact, inhalation, or ingestion — also poses a serious risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel as well as custodial settings and postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in resuscitation and adequate provision of naloxone to reverse poisoning.

E4. Economic costs

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

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

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

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

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

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

Section F. Involvement of organised crime

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

No information has been received by Europol indicating production of acryloylfentanyl within the EU.

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

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

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

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

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

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

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

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

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

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

F7. Use of violence between or within criminal groups

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

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

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

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Annex 2. List of participants at the risk assessment meeting of *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl)

22 February 2017

A. Extended Scientific Committee

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Acting Chair of the Scientific Committee

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

Professor Dr Paul DARGAN
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Professor Dr Matthew HICKMAN
School of Social and Community Medicine, University of Bristol

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

Professor Dr Brice De RUYVER
Department of Criminal Law and Criminology, Ghent University, Faculty of Law, Ghent

Dr Fernando RODRÍGUEZ de FONSECA
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Professor Dr Rainer SPANAGEL
Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

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

Dr Robertas BADARAS
Centre of Toxicology, Faculty of Medicine, Vilnius University, Vilnius

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Dr Fabiano RENIERO
Directorate General Joint Research Centre, Directorate F – Health, Consumers and Reference Materials, Fraud Detection and Prevention (F.4), European Commission, Ispra

Dr Jean-Marc VIDAL
Specialised Scientific Disciplines Department, European Medicines Agency

Daniel DUDEK
Serious and Organised Crime Unit, Europol

Paul GRIFFITHS
Scientific Director, EMCDDA

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

B. Invited Experts

Dr Simon ELLIOTT
Alere Forensics, Worcestershire

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National Institute for Health and Welfare, Helsinki

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

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