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Acryloylfentanyl

EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl)

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

About this series

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

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

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1. Introduction

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

In September 2016, the EMCDDA and Europol examined the available information on the new psychoactive substance *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide, commonly known as acryloylfentanyl, through a joint assessment based upon the following criteria:

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

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

2. Information collection process

In compliance with the provisions of the Council Decision, on 7 September 2016 the EMCDDA and Europol launched a procedure for the collection of information on acryloylfentanyl, in order to prepare the Joint Report. The information was collected mainly through the Reitox National Focal Points in the Member States, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway, Iceland and Liechtenstein. The EMA also provided information as relevant to the centralised procedure for authorising medicinal products. The information collection process was largely concluded by 19 October 2016; additional information and

clarifications from some countries were received the following day after the deadline.

Information collected by Europol

Europol asked the Europol National Units to provide information on:

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

Europol received responses from 20 Member States ⁽²⁾.

Information collected by the EMA

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

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

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

⁽²⁾ In alphabetical order: Austria, Belgium, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Poland, Portugal, Slovenia, Spain, Sweden and United Kingdom.

⁽³⁾ Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia and Hungary provided a response in relation to human medicinal products. France and Latvia provided a response in relation to veterinary medicinal products.

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

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

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

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

Information collected by the EMCDDA

The EMCDDA collected information through:

1. a structured questionnaire to the Reitox National Focal Points. The EMCDDA received replies from all 28 Member States, as well as Turkey and Norway;
2. reports previously provided to the European Union Early Warning System, including EMCDDA–Europol Reporting Forms and Progress Reports and Final Reports;
3. routine monitoring of open source information;
4. a specific information request to the World Health Organization on whether or not acryloylfentanyl is under assessment by the United Nations system; and,
5. a search of open source information conducted specifically for the production of the Joint Report which included: scientific and medical literature, official reports, grey literature, internet drug discussion forums and related websites (hereafter, 'user websites'), and, online vendors selling acryloylfentanyl.

Thus, the information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part) ⁽⁵⁾. The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. Images of the seizures and collected samples reported to the EMCDDA and Europol are provided in Annex 1 and Annex 2.

⁽⁴⁾ Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia and Hungary provided a response in relation to human medicinal products. France and Latvia provided a response in relation to veterinary medicinal products.

⁽⁵⁾ The sections on chemistry, pharmacology and toxicology, dependence liability and abuse potential, and characteristics of users were produced based on a technical report prepared by Dr István Ujváry, under EMCDDA contract CT.16.SAT.0099.1.0.

3. Information required by Article 5.2 of the Council Decision

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

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

Chemical description and names

Acryloylfentanyl belongs to the 4-anilidopiperidine class of synthetic opioids. This class also includes fentanyl and acetylfentanyl ⁽⁶⁾, which are internationally controlled ⁽⁷⁾.

Acryloylfentanyl differs from fentanyl in the double bond present in the 2-position of the propane attached to the *N*-phenyl moiety and is therefore an unsaturated analogue of fentanyl.

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

The synthesis and antinociceptive activity of acryloylfentanyl were first described in 1981 (Zhu et al., 1981).

Commonly used names: acryloylfentanyl or acrylfentanyl

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

Chemical Abstracts names: *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl-2-propenamide

Other chemical names: *N*-(1-phenethylpiperidin-4-yl)-*N*-acryloylanilino-piperidine; *N*-(1-phenylethylpiperidin-4-yl)-*N*-phenylacrylamide

Other names and code names: 'akrylfentanyl' (Swedish), acryloyl-F, Acr-F, ACF ⁽⁸⁾

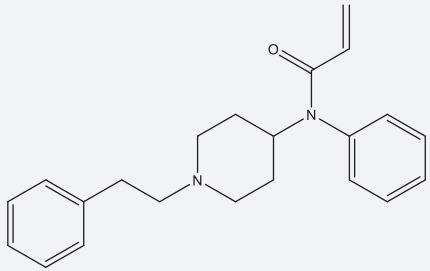
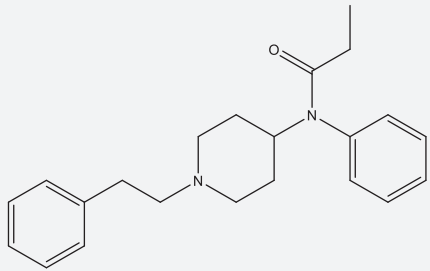
⁽⁶⁾ *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide.

⁽⁷⁾ Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs.

⁽⁸⁾ Important not to confuse 'ACF' with 'AF', which is one of the street names for acetylfentanyl.

FIGURE 1

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

		
	acryloylfentanyl	fentanyl
Molecular formula	C ₂₂ H ₂₆ N ₂ O	C ₂₂ H ₂₈ N ₂ O
Molecular mass	334.46	336.48

Chemical Abstracts Service (CAS) registry numbers ⁽⁹⁾:

82003-75-6: free amine

79279-03-1: hydrochloride salt

IUPAC International Chemical Identifier Key (InChI Key) ⁽¹⁰⁾:

RFQNLMWUIJJEQF-UHFFFAOYSA-N

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

Physical description

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

There is no solubility data on 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.

Acryloylfentanyl is expected to be highly lipophilic. Therefore, carry-over of traces of the substance during sample handling and analysis can be problematic (Degg, 2014).

Acryloylfentanyl has been typically seized in liquid or in tablet form. It has also been detected in powder form, and, in

a capsule in one case. A more detailed description of seizures and collected samples can be found in section 3.2.1 and section 3.2.2.

Detection and analysis

Gas Chromatography – Mass Spectrometry (GC-MS), Fourier Transform Infrared Spectroscopy (FT-IR) and Nuclear Magnetic Resonance (NMR) are available in the literature (Breindahl et al., 2016; Essawi, 1999; Slovenian National Forensic Laboratory, 2016).

Difficulties may be encountered in the analytical detection of acryloylfentanyl. Due to its close structural similarity with fentanyl, it is possible that immunoassays for fentanyl do not distinguish between the two compounds (Breindahl et al., 2016). Similarly, acryloylfentanyl is not expected give a response to tests developed for morphine-type opioids. There is no information on the reaction of acryloylfentanyl to presumptive colour tests.

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

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

⁽⁹⁾ The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.

⁽¹⁰⁾ InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

3.2.1 Information provided to Europol

Europol received replies from 20 Member States (Austria, Belgium, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Poland, Portugal, Slovenia, Spain, Sweden and United Kingdom).

The majority of countries who provided information to Europol reported that they have no available information on acryloylfentanyl. Since laboratory detection of this opioid is particularly challenging, the substance may not always be identified. For example, Belgium reported no detections of acryloylfentanyl but highlighted that, due to difficulties in forensic identification, it doesn't rule out the potential presence of the substance on the Belgian market.

Three countries provided information on acryloylfentanyl (Estonia, Finland and Sweden).

The level of production

No information was received in relation to the production of acryloylfentanyl. Estonia and Sweden informed Europol that acryloylfentanyl was ordered in powder form from China. According to information from Swedish authorities, the substance is then further handled by those involved in selling acryloylfentanyl, with the powder being used to make solutions. Those solutions are then placed into unmarked spray bottles of different colours, which are also sourced in China (see photos in Annex 2).

The level of distribution

Seizures were reported by 3 countries (Estonia, Finland and Sweden).

Estonia

Estonia reported 9 seizures of acryloylfentanyl (between June and 15 September 2016). All seizures were powders, with amounts ranging from 0.14 to 24.89 grams. The source of acryloylfentanyl seized in Estonia was reported as China. The substance was mainly purchased via the Internet and then either posted directly to Estonia or routed through other countries (for example Latvia).

Estonian authorities stated that the substance is consumed primarily by injection and that the use of nasal sprays has not been reported.

One death case was identified, which could be associated with acryloylfentanyl ⁽¹¹⁾.

⁽¹¹⁾ This case has not been reported to the EMCDDA.

Finland

Finland reported 1 seizure of several tablets containing acryloylfentanyl, which occurred in August 2016 (see photos in Annex 1).

Due to the nationality of the suspects involved in the seizure case and the geographic location where it took place (Åland Islands), Sweden was reported as the possible source for the seized tablets.

Sweden

Sweden reported that acryloylfentanyl was the most common fentanyl derivative for sale on the domestic illicit market from the end of January to September 2016, after which time it became scheduled as narcotic.

Nasal sprays containing various fentanyl derivatives were commonly sold on the surface internet from late 2015 onwards, most of which reportedly contained acryloylfentanyl.

Swedish authorities reported 36 fatalities to Europol associated with acryloylfentanyl, four of which are still under investigation.

In 2016, the Swedish authorities have seized an amount of 9.52 grams, 1595 mL and 856.5 units of acryloylfentanyl as liquids or tablets.

The level of trafficking

Information related to trafficking routes is limited to the seizures mentioned above.

3.2.2 Information provided to the EMCDDA

The EMCDDA received responses from all 28 Member States, as well as from Turkey and Norway. Of these, six Member States (Denmark, Estonia, Finland, Latvia, Slovenia and Sweden) reported detections of acryloylfentanyl ⁽¹²⁾. Images of the seizures and collected samples reported to the EMCDDA are provided in Annex 1.

It should be noted that the number of detections of acryloylfentanyl may be underestimated since the substance is not routinely screened for. Only two Member States (Finland in Sweden) reported that acryloylfentanyl is part of routine

⁽¹²⁾ '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.).

screening ⁽¹³⁾. The availability of a reference standard was not mentioned by any of the countries.

Seizures

In total, 95 seizures ⁽¹⁴⁾ have been reported to the EMCDDA by five Member States: Denmark (1 seizure), Estonia (9), Finland (1), Latvia (2), and Sweden (82). All the seizures were made in 2016 by Police or Customs. Most seizures have been made at street-level. Two seizures were made at a scene of death and 1 seizure was made in prison from incoming mail.

These seizures included:

- 49 seizures of liquids, all made in Sweden, amounting to a total of 1494 mL;
- 27 seizures of tablets (Sweden and Finland) amounting to 896 tablets. One of these seizures (99 blue oval tablets with no logos or markings seized in Finland), may be linked to a death.
- 18 seizures of powder amounting to 66.19 grams (Estonia, Latvia and Sweden). In Latvia, one of the seizures was made at a scene of death. Another seizure was made in prison from incoming mail (a package with light beige powder which was found inside a tube for cosmetic cream).
- 1 capsule, also containing triethylamine, seized in Denmark.

No quantitative information on purity was provided to the EMCDDA.

The capsule seized in Denmark contained acryloylfentanyl and triethylamine and some of the powders seized in Estonia contained acryloylfentanyl and sugars. For the remaining seizures, there is no information on whether other substances were also detected.

Collected samples

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

Biological samples

A total of 47 detections where acryloylfentanyl was analytically confirmed in biological samples were reported by two Member States: Denmark (1 sample) and Sweden (46).

These related to:

- 40 serious adverse events, all of them deaths, reported by Denmark (1) and Sweden (39) (see section 3.4.1);
- 6 cases related either to patients undergoing drug treatment (3) or cases related to persons suspected of having consumed drugs, committed minor offences, or crimes (3); and,
- 1 case of a person suspected of driving under the influence of drugs.

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

No information concerning organised crime involvement in the manufacture and/or trafficking of the acryloylfentanyl was provided by any of EU Member States.

Sweden reported that there are individuals involved in the illegal trade of acryloylfentanyl. Of these, two known vendors are linked to organised crime groups.

Money laundering aspects

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

In Sweden, online sales of fentanyl and its derivatives are reported to generate large profits. Acryloylfentanyl is sold on several Swedish websites on the surface internet.

Two Swedish websites where acryloylfentanyl has been sold, 'thesmack.biz' and 'RC24', had sales of 7 and 15 million Swedish Krona (SEK) respectively in 2015.

Violence in connection with production, wholesale and distribution

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

⁽¹³⁾ Information provided by the Member States, Turkey and Norway to the EMCDDA.

⁽¹⁴⁾ Many 'seizures' relate to individual cases, 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 Reports and Final Reports) and from individual EMCDDA–Europol Reporting forms submitted to the EMCDDA on an ad hoc basis.

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

3.4.1 Serious adverse events reported to the EMCDDA

Information about 63 serious adverse events ⁽¹⁵⁾ associated with acryloylfentanyl was reported to the EMCDDA by 4 Member States (Denmark, Finland, Latvia and Sweden). These cases comprised 21 acute intoxications and 42 deaths. An overview of these data is presented below.

Acute intoxications

Information about 21 acute intoxications associated with acryloylfentanyl was reported by Sweden. All the cases presented to hospital emergency departments. Information on whether acryloylfentanyl was analytically confirmed was not reported in any of the cases. The identification of the cases reported as non-fatal intoxications was made by the Swedish National Poisons Information Centre based on calls made to the centre. All the cases occurred between March and August 2016. 10 of the 21 cases were classified as non-fatal intoxications; in the remaining 11 cases the outcome of the intoxication was unknown.

Demographics

18 of the acute intoxications were male; 3 were female. For the cases for which the age was known, the ages ranged from 22 to 51 years old. The age was not known for 11 of the male patients. The mean age of the male cases for which an age was known was 35 years (median 29); the mean age for the female cases was 28 years (median 22).

Substances analytically identified

No analytical information is available regarding biological samples taken from the patients. The Poisons Information Centre has reported that in 6 cases there were indications that the patient may have ingested a substance other than acryloylfentanyl. Stimulants were reportedly taken in 4 out of the 6 cases (4-methylphenidate, the cathinones 4-Cl- α -PPP and N-ethylhexedrone, and amphetamine); in two cases the cathinones were injected. Opioids were reported in 1 case (oxycodone with buprenorphine). Benzodiazepines were registered in 2 cases.

⁽¹⁵⁾ Serious adverse event means any adverse event, whether analytically confirmed or not, that is associated with the consumption of a new psychoactive substance in a human that: results in death; is life-threatening; requires intensive treatment in an emergency room and/or requires hospitalisation; results in persistent or significant disability or incapacity; results in substance dependency or substance abuse; consists of a congenital anomaly or birth defect; or is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are: convulsions that do not result in hospitalisation.

It is important to note that this information is based on self reports rather than analytical results derived from physical samples.

Clinical features

Data on the clinical features ⁽¹⁶⁾ related to the 21 acute intoxications were generally consistent with opioid toxicity (in particular the opioid overdose triad). Other symptoms were reported, albeit less frequently.

Clinical features were reported for 19 out of 21 cases and no symptoms were reported in the remaining 2 cases. Reported symptoms included: unconsciousness (10 cases), respiratory depression (6), miosis (3), vomiting/nausea (3), tachycardia ⁽¹⁷⁾ (3), restlessness/anxiety (3), low oxygen saturation (2), dizziness (2) and hypertension (2). Features reported only once included: cyanosis, blurred vision, constipation, somnolence, tiredness, high body temperature ⁽¹⁸⁾, chest pain ⁽¹⁸⁾, hallucinations, muscular symptoms.

Naloxone was administered in 8 cases. In 4 of these cases, the patient was unconscious prior to administration, after which he/she woke up.

Seriousness and outcome

All cases required treatment in hospital. In 13 of the 21 cases, the seriousness of the intoxication was classified as life-threatening; the remaining cases were classified as not life-threatening.

In respect to the outcome of the intoxication:

- In 10 cases the patients were reported to have recovered; and,
- In 11 cases the outcome was unknown.

Route of administration

The route of administration was reported for 17 out of 21 cases. In 10 cases (58.8%) acryloylfentanyl was taken nasally using a nasal solution; in 3 cases (17.6%) it was taken orally or 'probably orally' as tablets; in 2 cases (11.8%) it was snorted (as a powder or presumably crushed tablets); in 1 case it was probably taken 'orally and snorted' (5.9%) using tablets and lastly in 1 case (5.9%) it was injected (as a nasal solution).

Name of the substance/product used

In all 21 cases reported to the Poisons Information Centre, the patient was reported to have taken 'akrylfentanyl', the Swedish name for acryloylfentanyl.

⁽¹⁶⁾ Includes an abnormal laboratory finding.

⁽¹⁷⁾ In all 3 cases, the patient was reported to have also taken a stimulant.

⁽¹⁸⁾ In this case, the patient was reported to have also taken a stimulant.

Source of the substance

Information on where the patients had sourced the substance was available in 4 cases: in all of them acryloylfentanyl was sourced from the internet.

Physical form

Information on the physical form of acryloylfentanyl used by the patients was available in 19 cases: 12 of them (63%) used a nasal solution; 5 of them used tablets (26%), 1 of them (5%) used a powder, and the remaining case was reported to have used both a nasal solution and tablets.

Amount or dose administered

The amount of acryloylfentanyl used by the patients was reported in 10 cases.

- In 5 cases, where the route of administration was nasal, the dose varied between 1 mg to 40 mg. The dosage regimen⁽¹⁹⁾ was not clear in all cases. In 2 cases the patient had been taking 20 mg/day; in another case the patient took 5-6 doses of 0.2 mg (time period not specified); in another case the patient took 4 doses of 10 mg (time period not specified).
- In 2 cases, where the route of administration was oral or 'probably oral', the doses reported were 0.3 mg (1/2 tablet) and 3.00 to 3.75 mg (4 or 5 tablets). The time period in which these doses were taken was not specified.
- In 2 cases, where the route of administration was snorting, the doses reported were 9 mg (15 tablets containing 0.6 mg of acryloylfentanyl) and 40 mg. The time period in which these doses were taken was not specified.
- In 1 case, where the route of administration was not known, the dose taken by the patient was 68 mg of acryloylfentanyl. The time period in which this dose was taken was not specified.

As mentioned above, it is important to note that acryloylfentanyl was not analytically confirmed from biological or physical samples taken from the patients and therefore these data should be taken as indicative only. Furthermore, quantities in the milligram scale are inherently prone to errors.

Analysis of the concentration of nasal spray solutions of acryloylfentanyl in Sweden suggests that a standard 10 mL spray bottle can usually contain 20 mg substance. A 10 mL bottle is deemed to be enough for 100 sprays (i.e. 0.2 mg/spray) (Helander, personal communication, October 2016).

Deaths

Information about 42 deaths associated with acryloylfentanyl was reported by four Member States: Denmark (1 case), Finland (1), Latvia (1) and Sweden (39). Acryloylfentanyl was analytically confirmed from biological samples taken from the decedents in 40 cases. In the remaining 2 cases, identification was made based on samples recovered from the scene of death (epidemiologically linked samples).

The discussion that follows will focus on the cases for which analytical confirmation from biological samples was obtained. These were: Denmark (1 case) and Sweden (39 cases).

Demographics

Of the 40 deaths, 34 were male (85%) and 6 were female (15%). The age of the decedents ranged from 19 to 54 years old. The mean age of the male decedents was 31 years (median 29.5); the mean age of the female decedents was 42 years (median 43).

Number of deaths by year

All deaths occurred in 2016 (April to September). Overall, 32 of the deaths (80%) occurred in the 3 summer months (June to August 2016), with 13 (32.5%) deaths taking place in August 2016.

Cause of death

The cause of death was reported in 33 cases. For the remaining 7 cases the cause of death was unknown at the time of reporting to the EMCDDA.

In 29 (88%) of the 33 cases where the cause of death was reported, acryloylfentanyl was either reported as the cause of death (24 cases) or as a contributing factor (5); in the remaining 4 cases an alternative cause of death was reported ('intoxication with narcotics'; 'intoxication with drugs (drug abuse)'; 'drug addiction' and 'suicide with several substances').

In 2 deaths acryloylfentanyl was the only substance detected; in both these cases acryloylfentanyl was reported as the cause of death. Other substances were detected in the remaining 38 deaths. These included: benzodiazepines and their metabolites, antidepressants, alcohol, antipsychotics, 'Z'-drugs, pregabalin and, to a lesser extent THC, cathinones, synthetic cannabinoids, amphetamine, MDMA, gabapentin. Opioids (including oxycodone and buprenorphine) were found in 3 out of 38 cases.

⁽¹⁹⁾ In this context, the 'dosage regimen' should be understood as the schedule of doses of acryloylfentanyl per unit of time.

Route of administration

The route of administration was known for 1 of the 40 deaths: in that case acryloylfentanyl was snorted.

Source

Information on where the decedents had sourced the substance was available in 1 case, in which the substance was obtained *via* an acquaintance.

Amount or dose administered

No information was reported on the amount of substance administered by the decedents.

3.4.2 Serious adverse events identified in open source information

No publications were found in open source information regarding fatal or non-fatal intoxications associated with analytically confirmed acryloylfentanyl.

3.4.3 Pharmacology

Overview

Published data on the pharmacology of acryloylfentanyl are limited to non-clinical studies. In vitro and animal studies 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.

Further research is required in order to have a more detailed understanding of the mode and mechanism of action of acryloylfentanyl, including its abuse liability and dependence potential, and how this relates to humans. This should also include study of the pharmacological effects of the metabolites of acryloylfentanyl.

Pharmacodynamics

In vivo data

There has been one single study in the scientific literature focusing on the binding of acryloylfentanyl to the opioid receptor. 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. Morphine, fentanyl and (+)-3-methylfentanyl were used as comparative standards.

TABLE 1

Opioid receptor binding data for morphine, fentanyl and its analogues (Maryanoff et al., 1982). The receptor affinity is expressed by IC₅₀ 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	[³ H]naltrexone
morphine	4.2	27
fentanyl	1.6	25
acryloylfentanyl	1.4	17
(+)-3-methylfentanyl	0.6	1.3

As seen in Table 1, the IC₅₀ values obtained for fentanyl and acryloylfentanyl were comparable; morphine was somewhat less effective in inhibiting the binding of radiolabeled receptor antagonists.

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.

Search in the PubChem Substance database for biological activity of acryloylfentanyl found 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)⁽²⁰⁾.

Animal studies

There have been two studies investigating the antinociceptive activity of acryloylfentanyl in the mouse (Zhu et al., 1981; Maryanoff et al., 1982).

The first publication mentioning acryloylfentanyl describes an extensive structure–activity relationship study involved 22 fentanyl analogues, and 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.

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

⁽²⁰⁾ 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 ⁽²¹⁾ (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

Essawi (Essawi, 1999) 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 comparative standards. 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 min and became insignificant at 90–100 min after treatment; 'at comparable doses, acryloylfentanyl maintained considerable analgesia at 90 and 120 min after administration. In its duration, the time-response profile of acryloylfentanyl resembled more closely that of morphine (20 mg/kg) than that of fentanyl'.

At 6.8 mg/kg and 17 mg/kg doses the antinociceptive effect of acryloylfentanyl was sustained for up to 4.5 hours without signs of opioid toxicity. At the 25 mg/kg dose, motor activity was inhibited, but the 'animals were not cataleptic and returned to continuous circling behaviour 3.5 hours after treatment'. However, at a dose of 50 mg/kg convulsions developed after 1 hour and '60% lethality was observed from apparent respiratory depression'.

Pre-administration by 30 min of 2 mg/kg naloxone blocked the antinociceptive effect of 0.85 mg/kg acryloylfentanyl for about 40 min when this antagonist effect disappeared and analgesia and other morphine-like effects could be noted for about 50 min.

Similar transient antagonist effect was observed when naloxone (2 mg/kg) was administered 40 min after acryloylfentanyl-treatment (0.85 mg/kg): the reversal of the antinociceptive effect lasted for 70 min, and then antinociception returned to the same level as before naloxone administration. It was concluded that acryloylfentanyl "has a mode of interaction with receptors different from morphine". Of the other three substances, the crotonoyl analogue only was slightly active.

Pharmacokinetics

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

No preclinical or human clinical studies were identified which focus on the pharmacokinetics, including metabolism, of acryloylfentanyl.

Based on structural and pharmacological similarity with fentanyl, acryloylfentanyl may be present in biological matrices mainly as its 'desphenethyl' derivative: 'acryloyl norfentanyl' (22).

A phenolic metabolite of acryloylfentanyl (23), if formed, may have some level of opioid activity and thus may contribute to the biological, including toxicological, properties of the parent substance.

Abuse liability and dependence potential

There are no data available from clinical studies on the dependence potential of acryloylfentanyl.

Limited information from self-reported user experiences on drug user websites indicates abuse potential and the development of tolerance.

(21) The median effective dose (ED₅₀) can be calculated by measuring the prolongation of latency times of a response to pain after administration of the test substance at various doses as compared to untreated control.

(22) Systematic name: *N*-phenyl-*N*-(piperidin-4-yl)prop-2-enamide. Molecular weight: 230.30

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

3.4.4 Toxicology

Animal data

There is limited information on the acute toxicity of acryloylfentanyl. In the mouse, the intraperitoneal injection of 25 mg/kg of the drug caused a transient suppression of motor activity; however, a dose of 50 mg/kg produced convulsions 1 hour after drug administration and '60% lethality was observed from apparent respiratory depression' (Essawi, 1999). From these data, an acute mouse LD50 value between 25 and 50 mg/kg upon intraperitoneal administration may be postulated. While no comparative standard was used in this particular study, other sources on fentanyl indicate that the acute toxicity of acryloylfentanyl is similar to that of fentanyl ⁽²⁴⁾.

There are no reports on the chronic toxicity of acryloylfentanyl.

Human data

There have been no studies on the human toxicity of acryloylfentanyl. However, the comparable pharmacology of acryloylfentanyl and fentanyl in preclinical studies both in vitro and in vivo suggests toxicological similarity. For fentanyl, the estimated human lethal dose could be as low as 2 mg when injected (Marquardt et al., 1995; Baselt, 2000; Reeves and Ginifer, 2002; Moffat et al., 2011).

Data from serious adverse events associated with acryloylfentanyl are discussed above (Section 3.4.1). Based on limited data, it appears that the toxidrome of acryloylfentanyl may be broadly similar to other fentanyls and narcotic-analgesic opioids. This includes the opioid overdose triad of miosis, unconsciousness, and respiratory depression.

3.4.5 Characteristics of users

Data on the characteristics of users of acryloylfentanyl is limited to information derived from reporting of serious adverse events (discussed in Section 3.4.1) and information available on online drug user forums related to self-reported user experiences.

It should be noted that the specific substance(s) used in the self-reported experiences provided in this report cannot be confirmed; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used by those posting their experiences on said forums. In addition, the information provided on user websites and from specific user groups may

not necessarily be representative of other users of acryloylfentanyl and should be regarded as illustrative only.

Route of administration

Acryloylfentanyl may be taken orally (as powder in capsules or tablets); nasally (as a spray, a powder or tablets); and by injecting a solution of the substance.

Self-reports available on online forums describe snorting or inhalation by smoking or vaporising the 'free base' of acryloylfentanyl but this route has not been reported by any of the Member States. Since the free base is poorly soluble in water, injecting users dissolve the homemade solution of the citrate salt of the drug; ethanol has also been used as co-solvent.

From the data reported to the EMCDDA, nasal sprays may be a common route of administration of acryloylfentanyl. These require that a solution of acryloylfentanyl is prepared either by the user directly or by the seller. It is unlikely that these solutions are prepared taking into account the effective and lethal dose for acryloylfentanyl, as these are not known from published studies. Moreover, the solutions themselves are prepared using small amounts of substance (for example 5 to 20 mg of acryloylfentanyl in 10 mL) ⁽²⁵⁾. Minor errors in dilution or weighing can therefore lead to significant variations in the concentration of acryloylfentanyl in solution, which can subsequently result in overdoses.

Settings of use

Data from serious adverse events reported to the EMCDDA suggests that acryloylfentanyl is used at home, with 20 (50%) out of 40 deaths having occurred in the decedents residence and a further 5 deaths occurring 'in bed'.

Limited data from users forums is also suggestive of home setting, but many users claim they can go about their daily lives while under the influence, and dose intermittently during the day, (e.g. at work).

Dose, re-dosing, drug regimens

As with all psychoactive substances, the dose required to attain the desired effects depends on the route of administration. The available data, however, does not allow the identification of common/typical doses of acryloylfentanyl regardless of route.

There are no clinical studies on the doses required to produce subjective effects of acryloylfentanyl in humans. Limited data reported to the EMCDDA suggests that doses of

⁽²⁴⁾ For comparison, reported mouse intraperitoneal LD50 values for fentanyl are 26.3 mg/kg (Vuckovic et al., 2011) and 17.5 mg/kg (Gupta et al., 2013); mouse intravenous LD50 values of 238 and 2.91 mg/kg fentanyl, respectively (Gupta et al., 2013); mouse oral LD50 values of 470, 62 and 9.3 mg/kg for morphine and fentanyl and acetylfentanyl, respectively (Higashikawa and Suzuki, 2008b).

⁽²⁵⁾ See for example: <https://www.flashback.org/t2671134> or <http://www.bluelight.org/vb/threads/715710-Acrylfentanyl>

acryloylfentanyl from 0.1 to 68 mg may be taken, administered orally or by nasal insufflation.

The time period in which these doses were taken was specified only in 2 cases. For these the route of administration was nasal. In one case the user was reported to have taken 20 mg of acryloylfentanyl daily 'for the last months' and in the second case the user was said to have used 20 mg acryloylfentanyl/day at (or around) the time of the intoxication, and that prior to that 'lower doses' were used for 'about 3 months'. It is important to note that in both these cases the consumption of acryloylfentanyl was not confirmed analytically from biological samples taken from the users.

In one online forum, users described starting with a 50/50 mixture of water/acryloylfentanyl and a dose of 2-3 sprays, after which they wait for the onset of effects. If nothing happens, users describe that they either spraying until a desired effect is reached. One user said he re-dosed with a couple of sprays every 2 hours or so during the day ⁽²⁶⁾.

User self-reports posted on Internet forums also mention sub-milligram doses administered by nasal spray as being psychoactive.

The available data suggests that polydrug use might be common in those using acryloylfentanyl.

Subjective, psychological, and behavioural effects

There are no human clinical studies assessing the psychological and/or behavioural effects of acryloylfentanyl in humans. From limited data available in drug user websites, the psychoactivity of acryloylfentanyl is similar to that of other opioids and characterised by relaxation and euphoria.

Effect on ability to operate machinery and drive

Based on limited data from non-clinical studies, serious adverse events, and self-reported user experiences, it may be assumed that the acute behavioural effects of acryloylfentanyl on operating machinery and driving are similar to those caused by other opioid-type narcotic-analgesics.

Availability, supply, price

Online vendors

A structured search by the EMCDDA of online vendors ⁽²⁷⁾ of acryloylfentanyl on the surface web ⁽²⁸⁾ was conducted in

October 2016. The search identified 9 vendors that appeared to be based in, and/or claim to have presence in China (n=6 sites), in Hong Kong (n=1), in India (n=1 sites) and in Denmark (n=1). 8 of the sites presented information in English and 1 site in Danish. Three of the sites only provided prices for acryloylfentanyl on application, two presented prices as 'negotiable' and one 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:

- on these sites acryloylfentanyl was typically sold as a 'research chemical';
- the minimum quantity offered was 1 mg (n=1 sites) with a price of EUR 2.70. Nonetheless the minimum order in this website is EUR 67;⁽²⁹⁾
- the maximum quantity offered was 500 g (n=1 sites) with a price of EUR 7,322;

Prevalence of use

No data from general population surveys or targeted surveys were found on the prevalence of use of acryloylfentanyl.

Information on the use of acryloylfentanyl in Europe is mostly limited to discussions on user websites. From these discussions, it appears that acryloylfentanyl is used by psychonauts and users with experience of other opioids.

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

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

On 15 September 2016, the World Health Organization informed the EMCDDA that acryloylfentanyl is currently not under assessment and has not been under assessment by the UN system.

⁽²⁶⁾ Source: <https://www.flashback.org/t2671134> (accessed: 24 October 2016).

⁽²⁷⁾ 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.

⁽²⁸⁾ 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.

⁽²⁹⁾ Prices listed in DKK were converted to EUR according to Google exchange rate from the 25.10.2016 (DKK 1 = EUR 0,13).

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

The first official EMCDDA–Europol notification of acryloylfentanyl dates from 7 July 2016 from the Danish National Focal Point. 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 *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP)⁽³⁰⁾, which can also be used for the synthesis of fentanyl. An impurity, triethylamine hydrochloride, was also detected by NMR analysis (see section 3.8.1 for more detailed information).

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

It is important to note that acryloylfentanyl has been detected on the European market since at least April 2016, as evidenced by a seizure of the substance in liquid form reported by the Swedish National Focal Point in August 2016.

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

Five Member States (Cyprus, Ireland, Latvia, Sweden and the United Kingdom) 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 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 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.

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⁽³¹⁾. 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 import of, trade in and marketing of acryloylfentanyl is controlled by the Medicines Act.

Twenty-one Member States (Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland⁽³²⁾, France, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, Malta, Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain) and Turkey reported that acryloylfentanyl is not subject to control measures at the national level.

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

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

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

⁽³¹⁾ Austria reported that 'Due to its phenethylamine 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>)'.

⁽³²⁾ Finland reported that the substance is proposed to be controlled as a narcotic; the scheduling is expected to come into force on 14 November 2016.

⁽³⁰⁾ 4-anilino-*N*-phenethylpiperidine.

The synthesis of acryloylfentanyl has been described in the literature. The two published synthetic methods for acryloylfentanyl describe the acylation of the precursor 4-ANPP^(33,34), with acryloyl chloride⁽³⁵⁾ (Maryanoff et al., 1982; Zhu et al., 1981) or 3-chloropropionyl chloride⁽³⁶⁾ (Essawi, 1999).

The detection of 4-ANPP in a seized sample of acryloylfentanyl in Denmark (section 3.6) and the availability of 4-ANPP on the chemicals market suggest its use as precursor in the manufacture of the acryloylfentanyl. In addition, the presence of triethylamine hydrochloride in the same sample indicates a possible modification of the Siegfried method, also used for the synthesis of fentanyl, using triethylamine as for the acetylation reaction instead of pyridine (Breindahl et al., 2016).

The manufacture of acryloylfentanyl relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl (Casy and Huckstep, 1988; Gupta et al., 2013; Zee and Wang, 1980). Therefore the methods developed for the synthesis of fentanyl are applicable to acryloylfentanyl but use a different acylating agent in the final acylation step.

Most of the synthetic procedures are straightforward, use common laboratory equipment and precursors, and detailed recipes are available on the Internet⁽³⁷⁾. While only basic knowledge of synthetic chemistry is required, due to the potency of fentanyl caution is required when carrying out the final synthetic step as well as when purifying and handling the substance⁽³⁸⁾. Likewise, skin contact with or inhalation of fentanyl pose a serious health hazard. In addition to exercising extreme caution, the multiple doses of the opioid antagonist naloxone, as an antidote to poisoning in an accidental exposure, should be available when handling materials suspected to contain these substances (CDCP, 2013; DEA, 2016).

The precursors *N*-phenethyl-4-piperidone (NPP) and 4-ANPP are offered from gram to bulk (multikilogram) quantities on the Internet from dozens of suppliers. For example, prices for the immediate precursor 4-ANPP range from USD 75 per 100 gram to USD 5000 per 1 kg.

Acryloylfentanyl could be potentially used as a precursor to fentanyl by saturating the double bond of the acrylamide moiety using catalytic hydrogenation (Huckle et al., 1972).

None of the synthetic precursors mentioned in this section are included in Table I or Table II of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988. 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).

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. There is no information on the actual method(s) used for the production of acryloylfentanyl that has been detected in Europe to date.

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

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

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

No information was provided by any Member State that indicated that acryloylfentanyl had any other use apart from in analytical reference materials and scientific research.

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

Fifteen countries (Austria, Croatia, Czech Republic, Denmark, Estonia, Finland, Greece, Hungary, Ireland, Malta, Netherlands,

⁽³³⁾ 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.

⁽³⁴⁾ 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.

⁽³⁵⁾ IUPAC name: prop-2-enoyl chloride, CAS RN: 814-68-6; European Community (EC) Number: 212-399-0

⁽³⁶⁾ IUPAC Name: 3-chloropropionyl chloride, CAS RN: 625-36-5; European Community (EC) Number: 210-890-4.

⁽³⁷⁾ 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>).

⁽³⁸⁾ Self-educated clandestine chemists commented on the risk while discussing the synthesis of fentanyl and its potent 3-methyl and α -methyl homologues (comment was posted on 7 May, 2002); available at: <https://the-hive.archive.erowid.org/forum/showflat.pl?Cat=&Number=260275> (Accessed: 6 October 2016).

Poland, Slovakia, Slovenia, and Spain) reported that acrylolyfentanyl is not used to manufacture a medicinal product for human use. Eight countries (Belgium, Germany, Iceland, Italy, Norway, Portugal, Sweden, and the United Kingdom) reported that it was unknown if acrylolyfentanyl is used to manufacture a medicinal product for human use.

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

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

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

4.1. Marketing authorization

Twenty-three countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) reported that acrylolyfentanyl has not been granted a marketing authorization as a medicinal product for human use.

Twenty-three countries (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) reported that acrylolyfentanyl has not been granted a marketing authorization as a medicinal product for veterinary use.

The EMA also reported that acrylolyfentanyl has not been granted a marketing authorization as a medicinal product for neither human nor veterinary use through the centralized procedure.

4.2. Application for a marketing authorization

Twenty-three countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) reported that acrylolyfentanyl is not the subject of an application for a marketing authorization as a medicinal product for human use.

Twenty-three countries (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) reported that acrylolyfentanyl is not the subject of an application for a marketing authorization as a medicinal product for veterinary use.

The EMA also reported that acrylolyfentanyl is not the subject of an application for a marketing authorization for neither human nor veterinary use through the centralized procedure.

4.3. Suspended marketing authorization

Twenty-three countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) reported that that there had been no cases of suspended marketing authorization in respect to acrylolyfentanyl as a human medicine.

Twenty-three countries (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) reported that that there had been no cases of suspended marketing authorization in respect to acrylolyfentanyl as a veterinary medicine.

The EMA also reported that acrylolyfentanyl is not the subject of a suspended marketing authorization for neither human nor veterinary use through the centralized procedure.

5. Conclusion

Acryloylfentanyl is a synthetic opioid. It is closely related to fentanyl, which is controlled under the United Nations Single Convention on Narcotic Drugs of 1961. Data suggests that acryloylfentanyl is likely to be a potent opioid narcotic analgesic and may have an abuse liability and dependence potential in humans; these effects may be broadly comparable to fentanyl.

Acryloylfentanyl has been available in the European Union since at least April 2016 and has been detected in 6 Member States. In most cases it has been seized as a liquid, but other forms such as tablets, powders and a capsule have also been detected. The detected quantities are relatively small; however, they should be taken in the context of the high potency of the substance.

There is no indication of illicit production sites within the European Union. Acryloylfentanyl seems to be sourced as a powder from China (routing through Latvia on one occasion). The powders were reported to be used in the making of solutions, which are then placed in nasal spray containers. One country reported that two individuals linked to organised crime groups were involved in the illicit trade of acryloylfentanyl.

Acryloylfentanyl is sold as a 'research chemical' online and is available in small and wholesale amounts. Due to its close structural similarity to fentanyl, acryloylfentanyl can theoretically be used as a precursor for fentanyl.

42 deaths associated with acryloylfentanyl have been reported by 4 Member States, of which 40 were analytically confirmed. In 29 of these deaths acryloylfentanyl was the cause of death or contributed to the death. All deaths occurred in 2016; 80% of them occurred within a period of three months. One Member State reported 21 acute intoxications, 13 of which were life threatening and required hospitalisation. The acute intoxications were not analytically confirmed.

Information on the use of acryloylfentanyl in Europe is limited. It appears that acryloylfentanyl is used as a drug in its own right.

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

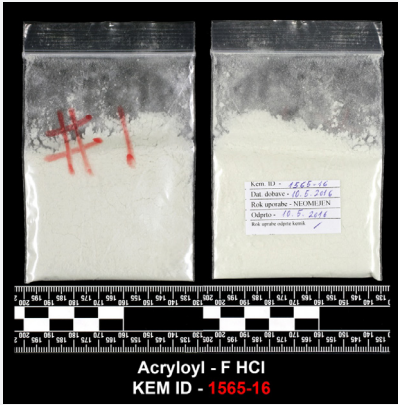

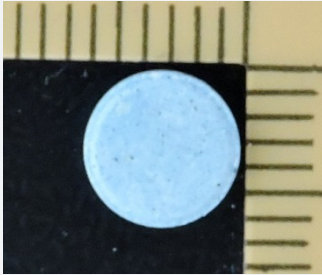
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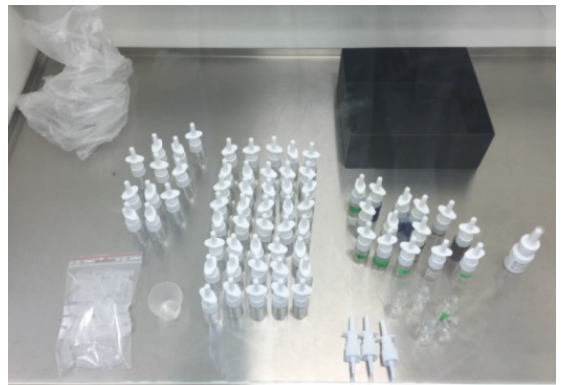
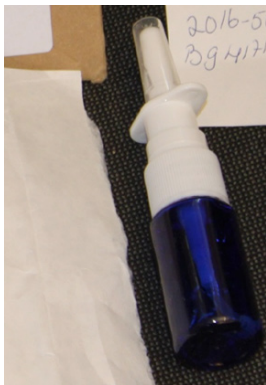
Annex 1

Images from seizures and collected samples provided to the EMCDDA.

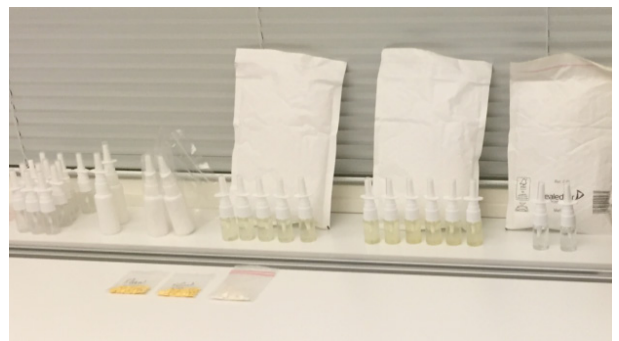
Country	Image	Description
Slovenia		<p>Collected sample, 10 May 2016 Light green powder Collecting authority: National Forensic Laboratory – test purchase in the frame of EU co-funded project RESPONSE</p>
Denmark		<p>Seizure, 11 May 2016 Capsule, seized in Aalborg Seizing authority: Dept. of Forensic Psychiatry, Aalborg Psychiatric Hospital</p>
Finland		<p>Seizure, 8 August 2016 Tablets, seized in Åland Seizing authority: Police</p>

Annex 2

Images provided to Europol. Samples of nasal spray bottles seized by Swedish authorities in different cases.







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The Joint Report represents a legal document, prepared in cooperation with the Council, EMA, and Commission and is published in the original version that has not been edited.

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

The EMCDDA's publications are a prime source of information for a wide range of audiences including: policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

Related publications and websites**EMCDDA**

| *European Drug Report 2016: Trends and developments*, 2016

| *Early-warning system on new psychoactive substances — operating guidelines*, 2017

EMCDDA and Europol

| *EMCDDA–Europol 2015 Annual Report on the implementation of Council Decision 2005/387/JHA*, Implementation reports, 2016

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