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Acetylfentanyl

EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] acetamide (acetylfentanyl)

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

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.

EUROPOL

EMCDDA–Europol
joint publication

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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 2015, the EMCDDA and Europol examined the available information on the new psychoactive substance *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacetamide, commonly known as acetylfentanyl, 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 acetylfentanyl satisfied criteria 1, 4, 6. The two agencies therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on acetylfentanyl as stipulated by Article 5.1 of the Council Decision.

2. Information collection process

In compliance with the provisions of the Council Decision, on 22 September 2015 the EMCDDA and Europol launched a procedure for the collection of information on acetylfentanyl, 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 3 November 2015; additional information and clarifications from some countries were received up to four weeks after this date.

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

Information collected by Europol

Europol asked the Europol National Units to provide information on:

- the level of production of acetylfentanyl in their country;
- the level of distribution of acetylfentanyl in their country;
- the level of trafficking of acetylfentanyl in their country, both for internal, transit or export purposes;
- the number of seizures of acetylfentanyl 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 acetylfentanyl in their country; and,
- any known aspect of violence and/or money laundering relating to the production and trafficking of acetylfentanyl.

Europol received responses from 10 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 acetylfentanyl has obtained a marketing authorisation;
- the new psychoactive substance acetylfentanyl 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 acetylfentanyl has been suspended.

Twenty-four 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.

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

([2]) In alphabetical order: Belgium, Bulgaria, Croatia, Cyprus, Finland, Germany, Hungary, Luxembourg, Portugal, and Slovakia.

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

information on whether the new psychoactive substance acetylfentanyl 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-four 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 acetylfentanyl 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 acetylfentanyl.

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. The conclusion of the Joint Report was prepared and agreed by the EMCDDA and Europol who are the two agencies responsible for the report.

([4]) Austria, Belgium, Denmark, Estonia, Germany, Greece, Hungary, Iceland, Ireland, Norway, Poland, Portugal, Sweden, and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia and Spain provided a response in relation to human medicinal products. The Czech Republic, France, Italy, Latvia, the Netherlands, Romania, Slovakia, and Slovenia 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 in cooperation with Dr István Ujváry.

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

Acetylfentanyl belongs to the phenylpiperidine class of synthetic opioids. This class also includes fentanyl which is controlled under the United Nations Single Convention on Narcotic Drugs of 1961 (Schedule I). Structurally, acetylfentanyl differs from fentanyl by one methyl group ($-CH_3$) ([6]).

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

Acetylfentanyl was first disclosed in patents by the Belgian company Research Laboratorium Dr. C. Janssen in the early 1960's (Janssen and Gardocki, 1964; Janssen, 1965; see also Janssen, 1962) ([7]). The analgesic activity of acetylfentanyl was first described in 1968 (Janssen and Van der Eycken, 1968).

Commonly used names: acetylfentanyl or acetyl fentanyl ([8,9]).

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

Chemical Abstracts names: N-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinylacetamide; 1-phenethyl-4-(*N*-phenylacetamido) piperidine; 1-phenethyl-4-(2-phenylacetamido)piperidine.

([6]) Which is why the substance is also called desmethyl fentanyl (i.e. desmethylated fentanyl).

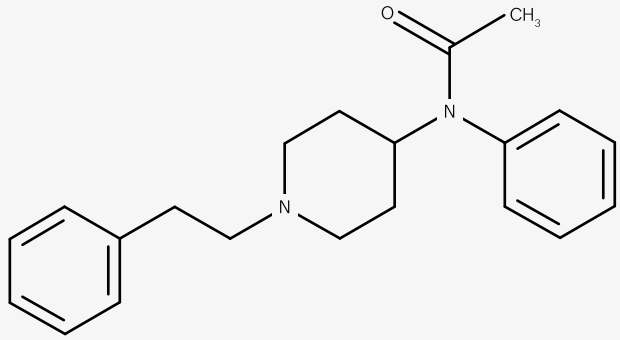
([7]) The first patent for this group of compounds was filed by (the now called) Janssen Pharmaceutica (US Patent 3,141,823 (July 21, 1964), N.V., 4 pages). The corresponding and frequently cited patent application by Janssen (Fr M 2340 of 27 April 1964; Chemical Abstract reference number: 62:14634) could not be located in the online French patent database.

([8]) Strictly speaking, neither name is correct: since fentanyl is a propionamide, so these two names actually refer to its acetylated derivative. A more appropriate designation would be 'despropionyl acetyl fentanyl'.

([9]) A related homologous compound is acetyl-α-methylfentanyl. Its systematic name: *N*-phenyl-1-(1-phenylpropan-2-yl)acetamide; CAS RN 101860-00-8. It is included in Schedule I of the United Nations Single Convention on Narcotic Drugs of 1961.

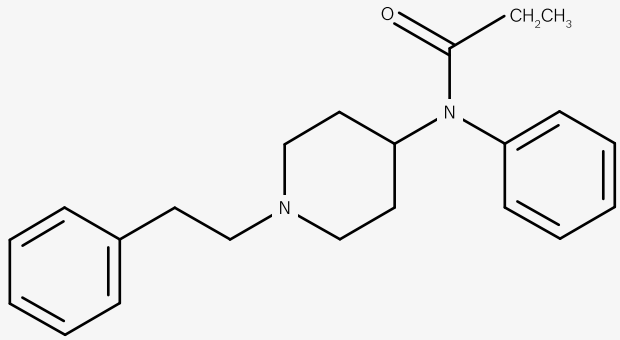
FIGURE 1

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



acetylfentanyl

Molecular formula: $C_{21}H_{26}N_2O$
Molecular mass: 322.44



fentanyl

Molecular formula: $C_{22}H_{28}N_2O$
Molecular mass: 336.47

Other chemical names: 1-phenethyl-4-(*N*-phenylacetamido) piperidine; *N*-(2-phenylethyl)-4-piperidylacetamide; *N*-[(1-(2-phenylethyl)-4-piperidyl]-*N*-phenylacetamide.

Other names and code names: desmethyl fentanyl; desmethylfentanyl; fentanyl acetyl analog; fentanyl related compound G; fentanyl impurity C; NIH 10485; MCV 4848.

According to data submitted to the EMCDDA, 'AF' is used as a street name for acetylfentanyl. Acetylfentanyl has also been found in a substance/product known as 'Valdiva' (Sweden). Other street names for acetylfentanyl that were identified from open source information are listed below. It is important to note that many of these names are often used in a generic way to describe any fentanil that appear on the drug market: a-fent, 'China White' (misleading), 'Apache', 'China girl', 'Dance fever', 'Friend', 'Goodfella', 'Jackpot', 'Murder 8', 'TNT', and 'Tango and Cash' ([10,11]).

([10]) These names were mentioned in news media: http://nationalpainreport.com/health-officials-warn-of-fatal-fentanyl-overdoses-8820632.html (posted June 27 2013).

([11]) The last three names were mentioned in news media: http://www.mirror.co.uk/news/uk-news/warning-over-legal-high-15-6619547 (12 October 2015)

Chemical Abstracts Service (CAS) registry numbers:

3258-84-2: free amine
117332-89-5: hydrochloride salt
638689-63-0: citrate salt

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

Acetylfentanyl contains one basic nitrogen atom in the piperidine ring thus readily forming salts with organic or inorganic acids. The hydrochloride salt of acetylfentanyl is described in the literature as a white powder. The large majority of seized powders reported to the EMCDDA were white or off-white in colour. To a lesser extent, light-brown and light pink powders were also seized. There has been at least one seizure and one collected sample reported to the EMCDDA where acetylfentanyl was in the hydrochloride salt form.

Acetylfentanyl is soluble in acidic media. According to information from a supplier of analytical reference materials 'acetyl fentanyl (hydrochloride)' is soluble in phosphate buffer saline (pH = 7.2): ~10 mg per ml; in ethanol: ~20 mg/ml; in DMF: ~10 mg/ml and in DMSO: ~10 mg/ml ([12,13]).

Acetylfentanyl has been typically seized in powder form or in tablet form. It has also been detected in liquids, and, to a lesser extent, in capsules. A more detailed description of seizures and collected samples can be found in section 3.2.1 and section 3.2.2.

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.

3.2.1. Information provided to Europol

Europol received replies from 10 Member States (Belgium, Bulgaria, Croatia, Cyprus, Finland, Germany, Hungary, Luxembourg, Portugal, and Slovakia).

The majority of countries who provided information to Europol reported that they have no available information on acetylfentanyl.

Slovakia and Germany reported that according to their intelligence acetylfentanyl is used among drug users, however so far no seizures took place in these countries.

In addition, Germany informed that searches made on the internet have revealed, that acetylfentanyl is already known and occasionally discussed among Anglophone drug users and sometimes is offered via the Internet.

Two Member States (Belgium and Finland) reported seizures of acetylfentanyl (see below).

The level of production

No information was received in relation to the production of acetylfentanyl.

The level of distribution

A total of seven seizures were reported to Europol: Belgium (4 seizures), Finland (3).

Belgium

The Belgian Customs Service reported four seizures from June 2015. The packages were seized based on the customs legislation, because of under estimated value provided or an alert was provided to the destination country. The total amount of substance seized was 114 g.

Details of seizures:

First case: acetylfentanyl sourced in China and destined to a private person in Finland. The substance was declared as acrylic paint phenolic resin. The weight of substance in powder form together with a plastic package was 2.36 g. Belgian Customs reported this shipment to Finland, where the seizure was made.

Second case: acetylfentanyl sourced in China and destined to a private person in France. The substance was found in the plastic package labelled as 'Hot melt powder'. The total weight of the substance and packaging material was 103.57 g. Custom services stopped the shipment because of under estimated value provided.

Third case: acetylfentanyl was sourced in China and destined to a private person in Germany. The substance was found in the small aluminium bag containing plastic package labelled as 'Hot melt powder '. The total weight of the substance and packaging material was 11.30 g. Custom services stopped the shipment because of under estimated value provided.

Fourth case: acetylfentanyl was sourced in China and destined to a private person in Germany. The shipment was declared as a pentaerythritol. Inside a double aluminium bag, there was a plastic package containing three plastic sachets each containing powders. The content of the first sachet was identified as propylfentanyl (n-propylfentanyl or i-propylfentanyl, also known as butanoylfentanyl or iso-butanoylfentanyl. Total weight including the plastic bag was 2.42 g. The second sachet contained 2.41 g of acetylfentanyl, and the third bag contained 2.40 g of flubromazepam.

([12]) Available at: https://www .caymanchem.com/msdss/ISO00128m.pdf (accessed: 12 October, 2015)

([13]) For an Internet forum discussion on the water solubility of acetylfentanyl, see: https://www.reddit.com/r/researchchemicals/comments/3c5voi/acetyl_fentanyl_water_soluble_or_no http://www.bluelight.org/vb/threads/724394-Acetyl-Fentanyl-Butry-Fentanyl-solubilities [sic]

Finland

Finland reported three minor postal seizures, which were seized in 2014. In two cases China was reported as the country of origin and in one case Belgium was reported as the country of origin. No further details concerning these seizures were provided to Europol.

The level of trafficking

Information related to trafficking routes is limited to the postal seizures mentioned above. In one of the cases, the package was sent from an address in Belgium, whereas in the remaining cases the packages originated from China.

Acetylfentanyl was destined for Finland in 4 cases, for Germany in 2 cases, and for France in 1 case.

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, eight Member States (Belgium, Finland, France, Germany, Poland, Spain, Sweden, and the United Kingdom), and Norway reported detections of acetylfentanyl ([14]).

Seizures

In total, 78 seizures ([15]) have been reported to the EMCDDA by seven Member States and Norway: Belgium (4 seizures), Finland (5), France (2), Germany (1), Poland (2), Sweden (62), the United Kingdom (1), and Norway (1).

Seizures have been made at street-level (including 2 seizures made at the scene of death), as well as at national borders (including postal seizures originating from China).

These seizures included:

- 38 seizures of powders, in quantities ranging from 0.04 to 252 g and colours varying between white/pink/beige/light brown;
- 12 seizures of liquids (including nasal sprays and tinctures) in quantities ranging from 3 to 290 mL. Liquids were all clear/colourless with the exception of 1 red liquid;
- 24 seizures of tablets, in quantities ranging from 1 to 69 units and colours varying between white/pink/red/beige/light blue/light green;
- 1 seizure of tablets and powders made at the scene of a death associated with acetylfentanyl. This included olive coloured round tablets with the imprint 'CDN' and '80' (reverse side), light blue round tablets with bisect bar and imprint 'A/215'; and, an oval beige tablet with imprint 'Phantom' and '100' (reverse side). All samples contained acetylfentanyl, ANPP, and lactose. Of note is that the imprints of 'CDN'/'80' and 'A/125' are also used on legitimate oxycodone-containing medicinal products. This finding may suggest that there are counterfeit medicinal products containing acetylfentanyl on the drug market;
- 1 seizure of powders and liquid made at the scene of a death associated with acetylfentanyl; and,
- 2 seizures of black-coloured capsules, one comprising of 10 units and the other of 18 units.

Overall, the material seized amounted to 458.8 g of powder, 454 tablets (and an additional 1.38 g of tablets in weight), 720 mL of liquids, and 28 capsules.

It should be noted that these seizures are likely to represent an under-detection of acetylfentanyl. In part this is because in some cases acetylfentanyl is only tested for by forensic laboratories when specifically requested or when there are specific reasons to do so ([16]).

Acetylfentanyl was the only substance detected in 92% of the reported seizures. In the remaining 8% of seizures, other substances were detected. This included opioids and stimulants. Briefly:

- Other opioids were found in 3 cases: one seizure of tablets contained acetylfentanyl and fentanyl; one seizure of a liquid (contained in a nasal spray) contained acetylfentanyl, U-47700, and butyrlfentanyl; a further seizure of liquid contained acetylfentanyl and U-47700.
- 4-ANPP([17]): this substance can be both a synthetic precursor or a metabolite of acetylfentanyl. It was found in two seizures of powders, as well as in a variety of tablets of different colours found at the scene of a death.
- Stimulants were present in 2 of the samples seized: in one case, α-PVP was the main constituent of the confiscated powder, and in another case traces of methamphetamine were found in a foil and spoon which were seized from the scene of death.

([14]) '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.)

([15]) 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 Reports and Final Reports) and from individual EMCDDA–Europol Reporting forms submitted to the EMCDDA on an ad hoc basis.

([16]) Information provided by the Member States, Turkey and Norway to the EMCDDA.

([17]) 4-anilino-*N*-phenylethylpiperidine.

No quantitative information on purity was provided to the EMCDDA. In one seizure and one collected sample, acetylfentanyl in powder form was reported as being 'almost pure' hydrochloride form.

Lactose (which may be used as an excipient/diluent) was detected in some of the tablets that were seized.

Collected samples

Two Member States reported a total of 5 samples containing acetylfentanyl which were collected from users: France (2 samples) and Spain (3). It is unknown where the users sourced the 2 samples reported by France. The 3 samples reported by Spain were purchased on the internet; in 2 of these cases it was reported to have been sold as butyr-fentanyl.

Biological samples

Four Member States (Germany, Poland, Sweden, and the United Kingdom) reported a total of 58 detections where acetylfentanyl was analytically confirmed in biological samples ([18]).

These related to:

- 40 serious adverse events (8 acute intoxications and 32 deaths);
- 16 cases related either to patients undergoing drug treatment or cases related to persons suspected of having consumed drugs, committed minor offences, or crimes; and,
- 2 cases of persons 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 was received in relation to the involvement of organised crime in the manufacture or trafficking of acetylfentanyl.

Money laundering aspects

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

([18]) A biological sample reported by Germany was excluded on the basis that there was no information reported in relation to the context of sampling.

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 acetylfentanyl.

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

Case-level data for 40 serious adverse events ([19]) associated with acetylfentanyl were reported to the EMCDDA by four Member States (Germany, Poland, Sweden, and the United Kingdom). These cases comprised 8 acute intoxications and 32 deaths. An overview of these data is presented below.

Acute intoxications

Case-level data for 8 acute intoxications associated with acetylfentanyl were reported by Sweden. All the cases presented to hospital emergency departments. Acetylfentanyl was analytically confirmed in all the cases. All the cases occurred in 2015. Six of the eight cases were classified as non-fatal intoxications; in the remaining two cases the outcome of the intoxication was unknown.

Demographics

Seven of the acute intoxications were male; one was female. The mean age of the male case was 26 years (median 27); the female case was aged 35.

Substances analytically identified

Alongside acetylfentanyl, benzodiazepines and/or their metabolites were detected in all 8 cases. Other substances were detected in 6 of the cases. These included: opioids and/or their metabolites; ethanol and metabolites; and stimulants.

([19]) 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.

Some of the substances that were detected included authorised medicinal products; it is unknown if these had been prescribed to the patients.

Clinical features

Data on the clinical features ([20]) related to the 8 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 all 8 cases. They included: unconsciousness (5 cases), miosis (4), respiratory depression (3), somnolence (2), rhabdomyolysis (2), hyperthermia (2), kidney failure (2). Features reported only once included: cardiac arrest, cyanosis, hypotension, aspiration pneumonia, urine retention, agitation, convulsions, slurred speech, tachycardia, and mydriasis.

Seriousness and outcome

In 7 of the 8 cases, the seriousness of the intoxication was classified as life-threatening; the remaining case was classified as not life-threatening but requiring treatment in hospital.

In respect to the outcome of the intoxication:

- In 5 cases the patients were reported to have recovered;
- In 1 case the patient was reported as recovering; and,
- In 2 cases the outcome was unknown.

Route of administration

The route of administration was only known for one case. Here, the patient was reported to have snorted acetylfentanyl as a powder.

Name of the substance/product used

The name of the substance taken by the patient was reported for 5 cases:

- in 3 cases the patients were reported to have taken 'acetylfentanyl';
- in 1 case, the patient was reported to have taken 'Xanor-stavar';
- in 1 case the patient was reported to have taken a powdered substance called 'Valdiva' which was sourced from the Internet apparently under this name (see below).

([20]) Includes an abnormal laboratory finding.

Source of the substance

Information on where the patients had sourced the substance was available in 3 cases: in all of them acetylfentanyl was sourced from the internet. In 1 of these cases it was reported that the substance was sourced as acetylfentanyl while in another case the substance was sourced as 'Valdiva'.

Physical form

Information on the physical form of acetylfentanyl used by the patients was available in 3 cases: 2 of them used a powder (one of which was reported to be 'Valdiva') and the remaining case was reported to have used tablets ('Xanor-stavar').

Amount or dose administered

No information was reported on the amount of acetylfentanyl used by the patients.

Deaths

Case-level data for 32 deaths associated with acetylfentanyl were reported by four Member States: Germany (2 cases), Poland (1) ([21]), Sweden (27), and the United Kingdom (2). Acetylfentanyl was analytically confirmed in all 32 cases.

Demographics

Of the 32 deaths, 26 were male (81%) and 6 were female (19%). The decedents ages ranged from 21 to 56 years old. The mean age of the male decedents was 32 years (median 31); the mean age of the female decedents was 37 years (median 34).

Number of deaths by year

One death occurred in 2013; 2 deaths occurred in 2014; 29 (90.6%) deaths occurred in 2015 (January–September). Overall, 13 (40%) deaths occurred in August 2015.

Cause of death

The cause of death was reported in 20 cases. For the remaining 12 cases the cause of death was unknown at the time of reporting to the EMCDDA.

In 19 of the 20 cases where the cause of death was reported, acetylfentanyl was either reported as the cause of death (11 cases) or as a contributing factor (8); in the remaining case an

([21]) The analytical confirmation of acetylfentanyl in the death reported by Poland is based on a preliminary report.

alternative cause of death was reported ('intoxication with narcotics').

In 2 deaths acetylfentanyl was the only substance detected; in both these cases acetylfentanyl was reported as the cause of death. Other substances were detected in the remaining 30 deaths. These included: benzodiazepines and their metabolites, opioids (including fentanyl and derivatives, and buprenorphine), antidepressants and antipsychotics, THC, synthetic cannabinoids, cocaine, amphetamine, methamphetamine, MDMA, methylphenidate, methoxetamine, α-PVT and MDPBP.

Route of administration

The route of administration was known for 3 of the 32 deaths: in two cases circumstantial evidence suggests that the acetylfentanyl was injected; in the third case the substance was presumed to be snorted.

Source

Information on where the decedents had sourced the substance was available in 3 cases: in all of them acetylfentanyl was sourced from the internet.

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

Since 2012, more than 50 deaths associated with acetylfentanyl have been reported in Russia (12 deaths) (Melen'tev et al., 2015) and in the United States of America (>40 deaths) (Drug Enforcement Administration, 2015a; Drug Enforcement Administration, 2015b; Centers for Disease Control and Prevention, 2013a; Centers for Disease Control and Prevention, 2013b; Lozier et al., 2015; Isenschmid et al., 2014; Isenschmid et al., 2015; McIntyre et al., 2015; Cunningham et al., 2015; Poklis et al., 2015; Zhang et al., 2015).

Investigations into these deaths suggest that those who use acetylfentanyl include individuals who use illicit opioids, such as heroin and/or prescription opioids.

3.4.3. Pharmacology

Overview

Published data on the pharmacology of acetylfentanyl are limited to nonclinical studies. These data suggests that acetylfentanyl is a potent and selective μ-opioid receptor agonist with some broad similarities to fentanyl.

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

Pharmacodynamics

In vivo and ex vivo data

Acetylfentanyl has been shown to bind to μ-opioid receptors in rat cerebrum membrane preparations (Woods et al., 1988). In a binding assay using a rat brain opioid receptor preparation and the non-selective opioid receptor agonist [^{3}H]etorphine as radioligand, the EC_{50} values ([22]) for morphine and acetylfentanyl were 23.6 and 676 nM, respectively, indicating that acetylfentanyl is about 25-times less potent than morphine as an opioid receptor ligand in this assay (Woods et al., 1988). In comparison, the EC_{50} value for fentanyl is 36.2 nM, indicating that fentanyl is somewhat less potent than morphine in this assay (Woods et al., 1998).

Pharmacological investigation of the degree of inhibition of electrically induced contractions of a mouse vas deferens preparation ([23]) showed that acetylfentanyl produces a more potent analgesic response in mice than that of morphine, but slightly less potent than fentanyl. In one study, acetylfentanyl was shown to display opioid receptor agonist activity with EC_{50} values of 4420 nM compared to 395 nM for morphine (Woods et al., 1988). The reported EC_{50} value for fentanyl was 37.1 nM (Woods et al., 1998).

The receptor selectivity of acetylfentanyl was also assessed by the MVD-assay in the presence of selective μ-opioid receptors (MOR) or δ-opioid receptor (DOR) antagonists (Woods et al., 1988). Pre-treatment of the mouse vas deferens preparation with the irreversible but non-competitive MOR-selective antagonist funaltrexamine the binding acetylfentanyl

([22]) EC_{50} refers to the half maximal effective molar concentration of a drug that produces 50% of its maximal possible effect.
([23]) Mouse vas deferens contains multiple opioid receptors and has been a traditional assay for opioid actions outside the central nervous system.

was unaffected ([^{3}H]etorphine-binding related EC_{50} value = 4800 nM) but the effect of acetylfentanyl on the inhibition of the electrically induced contractions of mouse vas deferens diminished (29.3%); furthermore, the selective DOR antagonist ICI-174864 failed to affect acetylfentanyl-inhibited etorphine binding (EC_{50} = 5170 nM) in the mouse vas deferens preparation. These experiments indicate that acetylfentanyl is a selective MOR agonist.

Animal studies

Acetylfentanyl is about 15 times more effective as an antinoceptive ([24]) agent than morphine, as shown by the acetic acid writhing test (Higashikawa and Suzuki, 2008). Potency of acetylfentanyl was about 3-fold less than that of fentanyl in this assay. The ED_{50} dose (the dose at which 50% of test animals had met the criterion for analgesic response) for acetylfentanyl, fentanyl and morphine were 0.021, 0.0061, and 0.33 mg/kg, respectively.

Pharmacokinetics

Due to its lipophilicity, acetylfentanyl, like fentanyl, is expected to readily cross the blood–brain barrier and also diffuse into fat and other tissues.

Nonclinical data on the metabolism of acetylfentanyl is not available. Published information from acetylfentanyl post-mortem cases (Finkelstein et al., 2015; Zhang et al., 2015; Cunningham et al., 2015; Hitsasune et al., 2015; K. Hitsasune, personal communication; Patton et al., 2014) as well as comparison to nonclinical data available for fentanyl (Goromaru et al., 1984; Guitton et al., 1997; DePriest et al., 2015) can provide some information as to the pharmacokinetics and metabolism of the substance.

Recently, the chemical structures of the main Phase I metabolites present in the urine of acetylfentanyl consumers have been determined (Melent'ev et al., 2015) and three key metabolic steps were proposed which involved hydroxylation (to give phenols), dealkylation (to give acetyl norfentanyl) and de-acetylation (to give 4-ANPP).

Limited information is available on the pharmacological effects of the metabolites acetylfentanyl. An early study by Schneider and Brune (1986) found that 4-ANPP and 4-anilinopiperidine, both of which are formed during the metabolism of acetylfentanyl, were less potent than fentanyl by four to five orders of magnitude. Compared to morphine, these two anilines were less active by three to four orders of magnitude. The only metabolite showing significant activity in this assay was a phenolic derivative hydroxylated at the 4-position of the phenylethyl moiety of fentanyl ([25]) the activity of which was found to lie between morphine and pethidine.

Accordingly, the corresponding phenolic metabolite of acetylfentanyl may have some level of opioid activity and thus contribute to the biological, including toxicological, properties of the parent substance.

Abuse liability and dependence potential

The dependence liability of acetylfentanyl in morphine-dependent rhesus monkeys was assessed in the 'single-dose suppression' (SDS) model of morphine withdrawal (Aceto et al., 1988). A dose of 0.5 mg/kg of subcutaneous injected acetylfentanyl briefly (for about 90 min) substituted completely for morphine; the effect of morphine injection in alleviating withdrawal symptoms lasted for a longer period. At peak effect, acetylfentanyl could thus be considered to be six-times as potent as morphine in this test.

No data are available from clinical studies on the abuse liability and dependence potential of acetylfentanyl in humans.

Limited information from self-reported user experiences on user websites appear to suggest an abuse potential and the development of tolerance.

Overall, the available data suggests that acetylfentanyl may have an abuse liability and dependence potential in humans.

3.4.4. Toxicology

Animal data

There is limited information on the toxicity of acetylfentanyl. In mice, the acute LD_{50} value of acetylfentanyl upon intraperitoneal injection is 9.3 mg/kg (Higashikawa and Suzuki, 2008). The LD_{50} values reported in the same study for morphine and fentanyl are 470 and 62 mg/kg, respectively, which suggests that acetylfentanyl is several times more toxic than fentanyl, at least in rodents ([26]).

The 'therapeutic index' (TI), (i.e. the ratio of the oral LD_{50} and ED_{50} values) for acetylfentanyl can be considered relatively small (440-fold) when compared to morphine (1420) and

([24]) Antinoceptive agent: refers to the ability that a substance has to inhibit nociception, i.e. to inhibit the sensation of pain.

([25]) Of the potential mono- and dihydroxylated metabolites only this substance was tested (that is N-{1-[2-(4-hydroxyphenyl)ethyl]piperidin-4-yl}-N-phenylpropionamide.

([26]) For comparison, the respective intravenous LD_{50} values in mice for morphine and fentanyl were found to be 270 and 11.2 mg/kg (Gardocki and Yelnosky, 1964).

fentanyl (10100). This indicates that the difference between the toxic dose and the effective antinociceptive dose for acetylfentanyl in mice is narrower than the respective differences for morphine and fentanyl ([27]).

Autopsy of the animals that died in the oral toxicity experiments revealed that there was significant bleeding in the small intestine, which was presumed to be one of the causes of death.

There are no reports on the chronic toxicity of acetylfentanyl.

Human data

Data from serious adverse events associated with acetylfentanyl are discussed above (Section 3.4.1). Based on limited data, it appears that the toxidrome of acetylfentanyl may be broadly similar to other fentanils 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 acetylfentanyl is limited.

It is important to note that when interpreting the data on self-reported user experiences that is provided in this report, it is not possible to confirm the specific substance(s) used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. In addition, the information provided on user websites and from specific user groups may not necessarily be representative of other users of acetylfentanyl and should be regarded as illustrative only.

Route of administration, dose, drug regimens and settings of use

Routes of administration include snorting, smoking/inhalation, oral (ingestion as powder, in capsules, tablets or as tinctures), nasal (using sprays), and injection (intravenous). Smokeable herbal preparations have also been noted in open source information but this route has not been reported by any of the Member States.

The salt form of acetylfentanyl is water soluble and therefore could be administered by injection. The free base is poorly soluble in water and can be smoked, vaporised or nasally administered ([28]).

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

Dose, re-dosing

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 acetylfentanyl regardless of route.

France reported a case where an individual self-reported having injected 10mg of acetylfentanyl, with a total of 30mg administered over a 12 hour period. The individual reported feeling 'on the verge of dying'.

There are no clinical studies on the doses required to produce subjective effects of acetylfentanyl in humans. Limited data from self-reported user experiences posted on user websites mention that doses of acetylfentanyl from 3 to 10mg are needed to notice 'opioid-like psychoactivity', administered either by injection or nasal insufflation.

Subjective, psychological, and behavioural effects

Discussions on user websites suggest that the subjective effects of acetylfentanyl are similar to that of other opioids and characterised by relaxation and euphoria (Gorodetzky and Martin, 1965). Nausea and vomiting have been mentioned as unintended effects. Information provided in some user experiences are consistent with symptoms of dependence ([29]).

There are no clinical studies assessing the psychological and/or behavioural effects of acetylfentanyl in humans. Limited data from serious adverse events and user websites suggest that the effects of acetylfentanyl resemble those of other narcotic-analgesic opioids.

Effect on ability to operate machinery and drive

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

([27]) These estimates are only applicable to oral administration in the experimental mice. The TI value could be different upon injection use in humans with the intention to achieve psychoactive effects.

([28]) See, for example http://www.bluelight.org/vb/threads/724394-Acetyl-Fentanyl-Butry-Fentanyl-solubilities or https://www.reddit.com/r/researchchemicals/comments/3qbk8i/acetylfentanyl_freebase_instead_of_hcl_help

([29]) https://drugs-forum.com/forum/showthread.php?t=180038

Availability, supply, price

Online vendors

A structured search by the EMCDDA of online vendors ([30]) of acetylfentanyl on the surface web ([31]) was conducted in November 2015. The search identified 8 vendors that appeared to be based in, and/or claim to have presence in China (n=5 sites) and India (n=1 sites). For the remaining 2 vendors there was no apparent location mentioned. Four of the sites only provided quantities and prices for acetylfentanyl on application. The remaining 4 sites listed quantities and prices. Briefly:

- on these sites acetylfentanyl was typically sold as a 'research chemical';
- the minimum quantity offered was 10 mg (n=1 sites) with a price of EUR 183.31;
- the maximum quantity offered was 1 kg (n=1 sites) with a price of EUR 7,000;
- 2 of the 4 sites listed prices for 1g, for which the mean price was EUR 23.50; and,
- 1 of the 4 sites listed prices for other quantities:
  - The price for 10g was EUR 159.8 (EUR 15.98/g);
  - The price for 100g was EUR 846 (EUR 8.46/g);
  - The price for 1kg was EUR 6580 (EUR 6.58/g);

Prices were listed in United States Dollars on all 4 sites ([32]).

A similar search had been conducted in July 2015 and identified 19 vendors that appeared to be based in, and/or claim to have presence in China (n=11 sites), the United States of America (n=3) and India (n=1). For the remaining 4 vendors there was no apparent location mentioned.

There was change in the legal status of acetylfentanyl in China (section 3.7) between the dates of the two searches, but it is not clear what effect this has had on the online availability of acetylfentanyl on the surface web.

Prevalence of use

There appear to be no data from general population surveys or targeted surveys on the prevalence of acetylfentanyl use.

([30]) 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 acetylfentanyl through online classified advertisements, social media, and user websites.

([31]) The search of online vendors of acetylfentanyl was performed on google.co.uk on 17/11/2015 using the search strings: 'buy acetylfentanyl'. 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.

([32]) Prices listed in USD were converted to EUR according to Google exchange rate from the 17.11.2015 (USD 1 = EUR 0,94).

Information on the use of acetylfentanyl in Europe is mostly limited to discussions on user websites ([33,34]). From these discussions, it appears that acetylfentanyl is used by psychonauts and users with experience of other opioids.

Information from open source information suggests that user groups in the United States of America include individuals who use illicit opioids, such as heroin and/or prescription 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 (WHO) is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the United Nations Single Convention on Narcotic Drugs of 1961 and the United Nations Convention on Psychotropic Substances of 1971.

On 24 November 2015, WHO informed the EMCDDA that acetylfentanyl is currently under assessment by the United Nations system. Specifically, WHO reported that a critical review of acetylfentanyl has been published and the substance was assessed at the Thirty-Seventh meeting of the WHO Expert Committee on Drug Dependence (ECDD) that was held 16–20 November 2015. A recommendation from the assessment had not been published at the time of drafting this Joint Report.

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 acetylfentanyl dates from September 2014 from the Polish National Focal Point. The Reporting Form details a seizure of 20.2 g of white powder, also containing 4-anilino-*N*-phenethylpiperidine (4-ANPP (a precursor used in fentanyl production) that was seized in March 2014 by the Polish Customs authorities in Warsaw, Poland. The identification and analytical characterisation was based on Gas

([33]) https://www.google.pt/search?client=safari&rls=en&q=site:www.bluelight.org+acetylfentanyl+OR+acetyl+fentanyl&ie=UTF-8&oe=UTF-8&gfe_rd=cr&ei=pTI0VYOsPIys8wfc2IDYAQ

([34]) https://www.google.pt/search?client=safari&rls=en&q=site:drugs-forum.com+acetylfentanyl+OR+acetyl+fentanyl&ie=UTF-8&oe=UTF8&gfe_rd=cr&ei=_TI0VaWQDYys8wfc2IDYAQ

chromatography-mass spectrometry (GC-MS)and Infrared (IR) spectroscopy.

Acetylfentanyl 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 data provided by Germany as part of the data collection process for the Joint Report suggests that acetylfentanyl has been present on the European drugs market since at least 2013, as evidenced by a seizure of the substance made at a scene of a death.

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)

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

- In Austria, acetylfentanyl has been listed in Annex 1 of the Narcotic Substances Regulation.
- In Cyprus, acetylfentanyl has been controlled since 2013 via a Regulatory Administrative Act, ΚΔΠ 162/13, within the updates of the law L29/77. It is controlled within the context of a generic clause which addresses all fentanyl chemical groups.
- In Estonia, acetylfentanyl has been added to drug control legislation since 8 June 2015.
- In Finland, acetylfentanyl is controlled as a narcotic substance and has been listed in Annex 4 (Liite 4) of drug control legislation since 28 September 2015.
- In Ireland, acetylfentanyl is controlled under schedule I of the Misuse of Drugs Regulation 1988 (S.I. 328 of 1988).
- In Latvia, acetylfentanyl is included in the first list of 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, acetylfentanyl has been placed under control, according to the Republic of Lithuania Minister of Health Order No V-1062 (21/09/2015) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000 'On approval of the narcotic and psychotropic substances lists'.
- In Sweden, acetylfentanyl has been regulated since the 18 August 2015.
- In the United Kingdom, acetylfentanyl is controlled as a Class A substance under the Misuse of Drugs Act 1971 (Modification) Order 1986, No. 2230.

One Member State (Poland) reported that acetylfentanyl is controlled under specific new psychoactive substances control legislation. Specifically, acetylfentanyl 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 and trade in acetylfentanyl is controlled by the Medicines Act. Norway also reported that acetylfentanyl will be assessed for listing as a controlled substance (narcotic substance).

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

Finally, it is noteworthy that the People's Republic of China placed acetylfentanyl under national drug control legislation on the 1 October 2015.

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 acetylfentanyl which has been detected within Europe.

A limited number of publications describe the synthesis of acetylfentanyl (Janssen, 1965; Brine et al., 1989; Carroll et al., 1990; Fritschi and Klein, 1995; Valdez et al., 2014). In addition, there are several documented methods for the production of fentanyl in the scientific literature, which, in principle, could be applied to the synthesis of acetylfentanyl (provided that acetic acid anhydride or acetyl chloride is used in the acylation step). The direct conversion of fentanyl into acetylfentanyl would be circuitous thus impractical (Soine, 1986; Carroll and Brine,

1989; Hsu and Banks, 1992; Yadav et al., 2010; Vardanyan and Hruby, 2015).

Most of the synthetic procedures are straightforward and use common laboratory equipment, and only a basic knowledge of synthetic chemistry is required. Nonetheless, the final steps of purification and isolation of the products may pose significant risk to the operator due to the high potency of the final products.

Condensation of commercially available 1-benzyl-4-piperidinone ([35]) with aniline in the presence of an acid catalyst provides the corresponding imine (Schiff base), which is then reduced by lithium aluminum hydride to the 1-benzyl-*N*-phenylpiperidine-4-amine. Acylation of this anilinopiperidine with acetic acid anhydride affords *N*-(1-benzylpiperidin-4-yl)-*N*-phenylacetamide ([36]).

Removal of the benzyl protective group by catalytic hydrogenation using palladium-on-carbon catalyst is followed by alkylation of the piperidine with (2-haloethyl)benzene in the presence of an acid scavenger such as sodium carbonate to give acetylfentanyl.

More straightforward methods have been developed since then, including a 'one-pot' synthesis which is available online ([37]). This route (frequently called the 'Siegfried method') has not specifically been described in the literature. The detection of 4-ANPP as contaminant in seized samples of acetylfentanyl and the availability of this 4-ANPP on the chemicals market suggest its use as precursor in the manufacture of the acetylfentanyl (or, possible, other uncontrolled and yet undetected acyl analogues of fentanyl).

Lurie and co-workers (Lurie et al., 2012) suggest that the detection of *N*-benzylpiperidine-type contaminants, such as '*N*-benzyl-acetylfentanyl', in seized samples indicates that the substance was produced by the original Janssen method, while the presence of 4-ANPP as impurity in the samples suggests the use of the 'Siegfried method'.

Acetic anhydride, one of the precursors needed for the synthetic pathways described above, is included in the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

([35]) The three-step synthesis of N-benzylpiperidinone and other N-aralkylpiperidinones from benzylamine or the appropriate aralkylamine and ethyl (or methyl) acrylate is well documented.

([36]) A recent small seizure in Finland of N-(1-benzylpiperidin-4-yl)-N-(4-fluorophenyl)butanamide (or isomers) indicates the potential use of this route for the production of unregulated fentanyl analogues.Alternatively, such precursors can be offered on their own right as fentanyl analogues although limited information indicates that such N-benzyl piperidines are poorly active as analgesics (see, for example, Casy et al., 1969).

([37]) See, for example, http://opioids.com/fentanyl/synthesis.html

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 acetylfentanyl. 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 acetylfentanyl had any other use apart from in analytical reference materials and scientific research.

From the available information, it does not appear that acetylfentanyl 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.

Six countries (Austria, Denmark, Hungary, Poland, Spain, and the United Kingdom) reported that acetylfentanyl is not used to manufacture a medicinal product for human use. Eleven countries (Belgium, Croatia, Estonia, Germany, Greece, Iceland, Ireland, Norway, Portugal, Slovakia, and Sweden) reported that it was unknown if acetylfentanyl is used to manufacture a medicinal product for human use.

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

In addition, the EMA reported that it is not known if acetylfentanyl 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

Seventeen countries (Austria, Belgium, Croatia, Denmark, Estonia, Germany, Greece, Hungary, Iceland, Ireland, Norway, Poland, Portugal, Slovakia, Spain, Sweden, and the United Kingdom) reported that acetylfentanyl has not been granted a marketing authorization as a medicinal product for human use.

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

The EMA also reported that acetylfentanyl 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

Seventeen countries (Austria, Belgium, Croatia, Denmark, Estonia, Germany, Greece, Hungary, Iceland, Ireland, Norway, Poland, Portugal, Slovakia, Spain, Sweden, and the United Kingdom) reported that acetylfentanyl is not the subject of an application for a marketing authorization as a medicinal product for human use.

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

The EMA also reported that acetylfentanyl 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

Seventeen countries (Austria, Belgium, Croatia, Denmark, Estonia, Germany, Greece, Hungary, Iceland, Ireland, Norway, Poland, Portugal, Slovakia, Spain, Sweden, and the United Kingdom) reported that that there had been no cases of suspended marketing authorization granted in respect to acetylfentanyl as a human medicine.

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

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

5. Conclusion

Acetylfentanyl 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 acetylfentanyl 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.

Acetylfentanyl has been available in the European Union since at least 2013 and has been detected in 8 Member States and Norway. In most cases it has been seized as a powder, but other forms such as liquids and tablets have also been detected. The detected quantities are relatively small; however, there is still a cause for concern given the high potency of the substance. It appears that acetylfentanyl usually originates from chemical companies based China. There is no indication of illicit production sites within the European Union. Acetylfentanyl is sold as a 'research chemical' online and is available in wholesale and consumer amounts up to 1kg. Acetylfentanyl was controlled in China in October 2015 and there may have been a decrease in the number of internet vendors offering the substance for sale since that time.

40 serious adverse events associated with acetylfentanyl have been reported by 4 Member States. These comprise 8 acute intoxications requiring hospitalisation and 32 deaths; in 19 of these deaths acetylfentanyl was the cause of death or contributed to the death. More than 90% of the deaths occurred in 2015.

Information on the use of acetylfentanyl in Europe is limited. It appears that acetylfentanyl is used as a drug in its own right, but, given the experiences in the United States, concerns exist that the drug could be supplied surreptitiously to users, including those who inject opioids.

Acetylfentanyl is under assessment by the United Nations system — specifically, a critical review has been published and the drug was assessed at the 37th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that was held on 16–20 November 2015. A recommendation from the assessment has not been published at the time of writing this Joint Report.

We conclude that the health and social risks caused by the manufacture, trafficking and use of acetylfentanyl, 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. However, should the recommendation of the ECDD be published before or during the deliberations on this Joint Report, the Commission and the Council may wish to consider the implications of the recommendation when deciding on the need to request a risk assessment.

The EMCDDA and Europol will continue to intensively monitor acetylfentanyl in order to ensure that new information is provided to the Member States, the EMA, and the Commission via the information exchange of the European Union Early Warning System.

References

- Aceto, M., Bowman, E., Harris, L. and May, E. (1988), 'Dependence studies of new compounds in the rhesus monkey, rat, and mouse, 1987', in Harris, L. S. (ed.), *Problems of drug dependence*, NIDA Research Monograph 81, US Department of Health and Human Services, Rockville, Maryland, pp. 485–515.
- Brine, G. A., Boldt, K. G., Huang, P.-T., Sawyer, D. K. and Carroll, F. I. (1989), 'Carbon-13 nuclear magnetic resonance spectra of fentanyl analogs', *Journal of Heterocyclic Chemistry* 26 (3), pp. 677–86.
- Carroll, F. I. and Brine, G. A. (1989), '4-Phenylpiperidine analgesics, fentanyl and fentanyl analogues', in Klein, M., Sapienza, F., McClain, H., Jr. and Khan, I. (eds), *Clandestinely produced drugs, analogues and precursors*, US Department of Justice, Drug Enforcement Administration, Washington, DC, pp. 67–90.
- Carroll, F. I., Boldt, K. G., Huang, P.-T., Sawyer, D. K. and Brine, G. A. (1990), 'Synthesis of fentanyl analogs', in Harris, L. S. (ed.), *Problems of drug dependence 1989,* NIDA Research Monograph 95, US Department of Health and Human Services, Rockville, Maryland, pp. 497–8.
- Centers for Disease Control and Prevention (2013a), 'Acetyl fentanyl overdose fatalities — Rhode Island, March–May 2013', *MMWR* 62 (34), pp. 703–4.
- Centers for Disease Control and Prevention (2013b), 'Recommendations for laboratory testing for acetyl fentanyl and patient evaluation and treatment for overdose with synthetic opioid', CDC Health Alert Advisory, 20 June (emergency.cdc.gov/han/han00350.asp).
- Cunningham, S. M., Bailey, K. M., Newsome-Sparks, C. L., Gebhardt, M. A., Venuti, S. E., Haikal, N. A. and Kraner, J. C. (2015), 'Fatal intoxication with acetyl fentanyl — K27', 67th Annual Scientific Meeting Orlando, FL, American Academy of Forensic Sciences.
- DePriest, A. Z., Puet, B. L., Holt, A. C. and Cone, E. J. (2015), 'Metabolism and disposition of prescription opioids: a review', *Forensic Science Reviews* 27 (2), pp. 115–45.
- Drug Enforcement Administration (2010), 'Control of immediate precursor used in the illicit manufacture of fentanyl as a Schedule II Controlled Substance', *Federal Register* 75 (124), 37295–37299, 29 June (www.gpo.gov/fdsys//pkg/FR-2015-07-17/pdf/2015-17563.pdf).
- Drug Enforcement Administration (2015a), 'Schedules of controlled substances: temporary placement of acetyl fentanyl into Schedule I', *Federal Register* 80 (137), 42381–42385, 17 July (www.gpo.gov/fdsys//pkg/FR-2015-07-17/pdf/2015-17563.pdf).
- Drug Enforcement Administration (2015b), 'Acetyl fentanyl: background information and evaluation of "Three Factor Analysis" (Factors 4, 5 and 6) for temporary scheduling', Springfield, VA, Office of Diversion Control, Drug Enforcement Administration, 27 April (www.regulations.gov/contentStreamer?documentId=DEA-2015-0009-0002).
- Finkelstein, M. J., Chronister, C. W., Stanley, C., Ogilvie, L. M. and Goldberger, B. A. (2015), 'Analysis of acetyl fentanyl in postmortem blood and urine specimens by gas chromatography/mass spectrometry (GC/MS)', presented at the 67th Annual Scientific Meeting of the American Academy of Forensic Sciences, Orlando, FL, 16–21 February.
- Fritschi, G. and Klein, B. (1995), 'Zwischen- und Nebenprodukte bei der illegalen Herstellung von Fentanyl und Fluorfentanylen und die Synthese ihrer Acetylhomologen', *Archiv für Kriminologie* 196 (5–6), pp. 149–55.
- Gardocki, J. F. and Yelnosky, J. (1964), 'A study of some of the pharmacologic actions of fentanyl citrate', *Toxicology and Applied Pharmacology* 6 (1), pp. 48–62.
- Gorodetzky, C. W. and Martin, W. R. (1965), 'A comparison of fentanyl, droperidol, and morphine', *Clinical Pharmacology and Therapeutics* 6 (6), pp. 731–9.
- Goromaru, T., Matsuura, H., Yoshimura, N., et al. (1984), 'Identification and quantitative determination of fentanyl metabolites in patients by gas chromatography–mass spectrometry', *Anesthesiology* 61 (1), pp. 73–7.

Guitton, J., Désage, M., Alamercery, S., Dutruch, L., Dautraix, S., Perdrix, J. P. and Brazier, J. L. (1997), 'Gas chromatographic–mass spectrometry and gas chromatographic–Fourier transform infrared spectroscopy assay for the simultaneous identification of fentanyl metabolites', *Journal of Chromatography* 59 (1), pp. 59–70.

Higashikawa, Y. and Suzuki, S. (2008), 'Studies on 1-(2-phenethyl)-4-(N-propionylanilino)piperidine (fentanyl) and its related compounds. VI. Structure–analgesic activity relationship for fentanyl, methyl-substituted fentanyls and other analogues', *Forensic Toxicology* 26 (1): 1–5.

Hisatsune, K., Zaitsu, K., Kusano, M., Yamanaka, M., Nakajima, J., Moriyasu, T., Ishiba, A, Hida, M., Tsuchihashi, H. and Ishii, A. (2015), 'Determination of newly encountered designer drugs α-PHP and acetylfentanyl in an acute intoxication case by LC/Q-TOFMS', presented at the 53rd Annual Meeting of the International Association of Forensic Toxicologists, Firenze, Italy, 30 August–4 September.

Hsu, F.-L. and Banks, H. D. (1992), 'Fentanyl synthetic methodology: a comparative study', unclassified report No. CRDEC-TR-334, Edgewood Research, Development & Engineering Center, Aberdeen Proving Ground, Maryland (www.dtic.mil/dtic/tr/fulltext/u2/a250611.pdf).

Isenschmid, D. (2015), 'Case findings in acetyl fentanyl and combined heroin and fentanyl-related deaths' (nmslab.com/about-presentations-Fentanyl-Heroin-2015).

Isenschmid, D., Kacinko, S. and Logan, B. (2014), 'Case findings in 18 in acetylfentanyl related deaths', presented at the World Forensic Festival 2014, 12–18 October, Seoul, Korea (www.wff2014korea.org/upload/WFF2014_Abstract_Book.pdf).

Janssen, P. A. J. (1962), 'A review of the chemical features associated with strong morphine-like activity', *British Journal of Anaesthesia* 34 (4), pp. 260–8.

Janssen, P. A. J. (1965), '1-Aralkyl-4-(N-aryl-carbonyl amino)piperidines and related compounds', US Patent 3,164,600, 5 January, assigned to Research Laboratorium Dr. C. Janssen N.V.; see also: CA 62:14634e (1965).

Janssen, P. A. J. and Gardocki, J. F. (1964), 'Method for producing analgesia', US Patent 3,141,823 (21 July), assigned to Research Laboratorium Dr. C. Janssen N.V.

Janssen, P. A. J. and Van der Eycken, C. A. M. (1968), 'The chemical anatomy of potent morphine-like analgesics', in Burger, A. (ed.), *Drugs Affecting the Central Nervous System* Vol. 2., Marcel Dekker, Inc., New York, pp. 25–60.

Lozier, M. J., Boyd, M., Stanley, C., Ogilvie, L., King, E., Martin, C. and Lewis, L. (2015), 'Acetyl fentanyl, a novel fentanyl analog, causes 14 overdose deaths in Rhode Island, March–May 2013', *Journal of Medical Toxicology* 11 (2), pp. 208–17.

Lurie, I. S., Berrier, A. L., Casale, J. F., Iio, R and Bozenko, J. S., Jr. (2012), 'Profiling of illicit fentanyl using UHPLC–MS/MS. *Forensic Science International* 220(1-3):191-196.

McIntyre, I. M., Trochta, A., Gary, R. D., Malamatos, M. and Lucas, J. R. (2015), An acute acetyl fentanyl fatality: a case report with postmortem concentrations', *Journal of Analytical Toxicology* 39 (6), pp. 490–4.

Melent'ev, A. B., Kataev, S. S. and Dvorskaya, O. N. (2015), 'Identification and analytical properties of acetyl fentanyl metabolites', *Journal of Analytical Chemistry* 70 (2), pp. 240–8.

Patton, A. L., Seely, K. A., Pulla, S., Rusch, N. J., Moran, C. L., Fantegrossi, W. E., Knight, L. D., Marraffa, J. M., Kennedy, P. D., James, L. P., Endres, G. W. and Moran, J. H. (2014), 'Quantitative measurement of acetyl fentanyl and acetyl norfentanyl in human urine by LC-MS/MS', *Analytical Chemistry* 86 (3), pp. 1760–6.

Poklis, J., Poklis, A., Wolf, C., Mainland, M., Hair, L., Devers, K., Chrostowski, L., Arbefeville, E., Merves, M. and Pearson, J. (2015), 'Postmortem tissue distribution of acetyl fentanyl, fentanyl and their respective nor-metabolites analyzed by ultrahigh performance liquid chromatography with tandem mass spectrometry', *Forensic Science International* (in press). doi: 10.1016/j.forsciint.2015.10.21.

Prodduturi, S., Smith, G. J., Wokowich, A. M., Doub, W. H., Westenberger, B. J. and Buhse, L. (2009), 'Reservoir based fentanyl transdermal drug delivery systems: effect of patch age on drug release and skin permeation', *Pharmaceutical Research* 26(6), pp. 1344–52.

- Schneider, E. and Brune, K. (1986), 'Opioid activity and distribution of fentanyl metabolites', *Naunyn-Schmiedeberg's Archives of Pharmacology* 334 (3), pp. 267–74.
- Soine, W. H. (1986), 'Clandestine drug synthesis', *Medicinal Research Reviews* 6 (1), pp. 41–74.
- Valdez, C. A., Leif, R. N. and Mayer, B. P. (2014), 'An efficient, optimized synthesis of fentanyl and related analogs', *PLoS ONE* 9 (9), e108250.
- Vardanyan, R. S. and Hruby, V. J. (2015), 'Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications', *Future Medicinal Chemistry* 6 (4), pp. 385–412.
- Woods, J., Medzihradsky, F., Smith, C., Winger, G. and Gmerek, D. (1988), 'Evaluation of new compounds for opioid activity: 1987 annual report', in Harris, L. S. (ed.), *Problems of Drug Dependence, 1987: Proceedings of the 49th Annual Scientific Meeting*, NIDA Research Monograph Series 81, US Department of Health and Human Services, Rockville, Maryland, pp. 543–90.
- Woods, J., Medzihradsky, F., Smith, C., Winger, G. and Traynor, J. R. (1998), 'Evaluation of new compounds for opioid activity (1997)', in *Problems of Drug Dependence, 1997: Proceedings of the 59th Annual Scientific Meeting*, NIDA Research Monograph Series 178, US Department of Health and Human Services, Rockville, Maryland, pp. 408–28.
- Yadav, P., Chauhan, J. S., Ganesan, K., Gupta, P. K., Chauhan, D. and Gokulan, P. (2010), 'Synthetic methodology and structure activity relationship study of N-[1-(2-phenylethyl)-piperidin-4-yl]-propionamides', *Der Pharmacia Sinica* 1 (3), pp. 126–39.
- Zhang, X., Jufer Phipps, R., Levine, B. S., Aronica, P., Locke, J., Brassell, M. A., Warren, W. S., Ripple, M. G. and Fowler, D. R. (2015), 'Postmortem distribution of acetyl fentanyl', 67th Annual Scientific Meeting, Orlando, FL, American Academy of Forensic Sciences, Colorado Springs, CO.

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