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Carfentanil

EMCDDA–Europol Joint Report on a new psychoactive substance: methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl) amino]piperidine-4-carboxylate (carfentanil)

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 May 2017, the EMCDDA and Europol examined the available information on the new psychoactive substance methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino] piperidine-4-carboxylate, commonly known as carfentanil, 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 carfentanil satisfied criteria 1, 4, 5, and 6. The two agencies therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on carfentanil as stipulated by Article 5.1 of the Council Decision.

2. Information collection process

In compliance with the provisions of the Council Decision, on 18 May 2017 the EMCDDA and Europol launched a procedure for the collection of information on carfentanil, in order to prepare the Joint Report. The information was collected mainly through the Reitox national focal points in the Member States 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 29 June 2017.

Information collected by Europol

Europol asked the Europol national units to provide information on:

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

Europol received responses from 18 Member States ⁽²⁾ and Canada.

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 carfentanil has obtained a marketing authorisation;
- the new psychoactive substance carfentanil 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 carfentanil has been suspended.

Twenty-one 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

⁽²⁾ In alphabetical order: Austria, Belgium, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, Poland, Romania, Slovakia, Slovenia, Sweden, and the United Kingdom.

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

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

products in the European Union, the EMA also requested information on whether the new psychoactive substance carfentanil 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-one 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:

- a structured questionnaire to the Reitox national focal points. The EMCDDA received replies from 28 Member States and Norway ⁽⁵⁾;
- reports previously provided to the European Union Early Warning System, including EMCDDA–Europol Reporting Forms and Progress Reports and Final Reports;
- routine monitoring of open source information;
- a specific information request to the World Health Organization on whether or not carfentanil is under assessment by the United Nations system; and,
- 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 carfentanil.

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). The information included in sections 3.8.3 (in part) and 4 was provided by the EMA.

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

Carfentanil ⁽⁶⁾ belongs to the 4-anilidopiperidine class of synthetic opioids. This class also includes fentanyl ⁽⁷⁾, which is internationally controlled, and a number of other fentanils ⁽⁸⁾.

A total of 15 fentanils are controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol ⁽⁹⁾.

Carfentanil differs from fentanyl due to the presence of a methyl acetate attached at the 4-position of the piperidine moiety.

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

Carfentanil, which is also known as 4-carbomethoxyfentanyl, has two positional isomers, 2- and 3-carbomethoxyfentanyl ⁽¹⁰⁾. The positional isomers of carfentanil differ in the position of the methyl acetate on the piperidine ring. The synthesis and characterisation of 3-carbomethoxyfentanyl is reported in the literature (Mićović et al., 1998).

The synthesis of carfentanil was described in the 1970s (Van Daele et al., 1976).

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

⁽⁵⁾ A reply was not received from Turkey.

⁽⁶⁾ Also known as carfentanyl.

⁽⁷⁾ *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide.

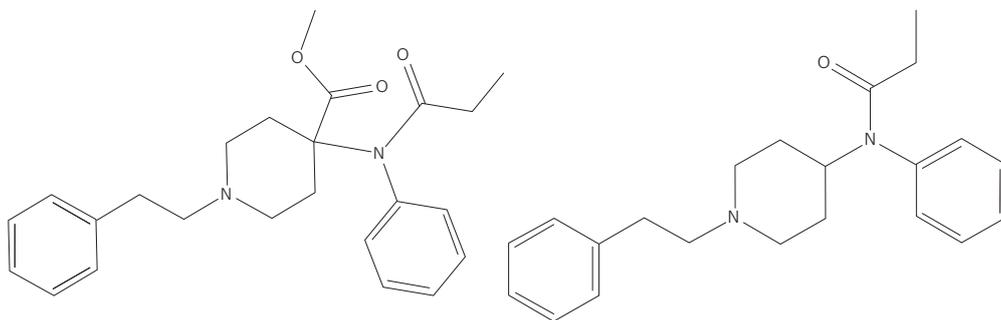
⁽⁸⁾ In this report, the term 'fentanils' is used to describe fentanyl and other substances structurally related to fentanyl.

⁽⁹⁾ 3-Methylfentanyl, 3-methylthiofentanyl, acetyl-alpha-methylfentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, para-fluorofentanyl, thiofentanyl, acetylthiofentanyl and butyrfentanyl are controlled under Schedule I and IV; alfentanil, fentanyl, sufentanil and remifentanil are controlled under Schedule I.

⁽¹⁰⁾ Note that although 'carfentanil' can refer to 2-, 3-, and 4-carbomethoxyfentanyl, in this report it will reference the 4-isomer.

FIGURE 1

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



	carfentanil	fentanyl
Molecular formula	C ₂₄ H ₃₀ N ₂ O ₃	C ₂₂ H ₂₈ N ₂ O
Molecular mass	394.52	336.48

Commonly used names:

carfentanil or carfentanyl

Systematic (IUPAC) name:

methyl 1-(2-phenylethyl)-4-[phenyl(propionoyl)amino]piperidine-4-carboxylate

Other chemical names:

methyl 1-(2-phenylethyl)-4-(N-propanoylanilino)piperidine-4-carboxylate;
 methyl 1-(2-phenylethyl)-4-[phenyl(propionyl)amino]-4-piperidinecarboxylate;
 methyl 1-(2-phenylethyl)-4-[phenyl(propionyl)amino]piperidine-4-carboxylate;
 methyl 1-phenethyl-4-(N-phenylpropionamido)piperidine-4-carboxylate;
 methyl 1-phenylethyl-4-(N-phenylpropionamido)isonipecotate;
 methyl 4-[phenyl(propionoyl)amino]-1-(2-phenylethyl)piperidine-4-carboxylate;
 methyl 4-[(1-oxopropyl)phenylamino]-1-(2-phenylethyl)-4-piperidinecarboxylate;
 1-phenethyl-4-(N-propionyl-anilino)-piperidine-4-carboxylic acid methyl ester;
 4-[(1-oxopropyl)phenylamino]-1-(2-phenylethyl)-4-piperidinecarboxylic acid methyl ester;
 4-methoxycarbonylfentanyl;
 4-carbomethoxyfentanyl;
 3-demethyllofentanil

International Nonproprietary Names (INN):

Carfentanilum (Latin) ⁽¹¹⁾
 Carfentanil (English) ⁽¹²⁾

Other names and code names:

Carfentanila (Spanish); R33799; NIH 10570; R 31 833; R31833

Proprietary names:

Wildnil ⁽¹³⁾

Street names:

'C.50' ⁽¹⁴⁾

Chemical Abstracts Service (CAS) registry numbers ^(15,16):

59708-52-0 free base
 61086-44-0 oxalate salt
 61380-27-6 citrate salt

IUPAC International Chemical Identifier Key (InChI Key) ⁽¹⁷⁾:

YDSDEBIZUNNPOB-UHFFFAOYSA-N

⁽¹¹⁾ <http://www.who.int/medicines/publications/druginformation/innlists/RL18.pdf?ua=1>

⁽¹²⁾ <http://www.who.int/medicines/publications/druginformation/innlists/RL18.pdf?ua=1>

⁽¹³⁾ Wildnil® is the proprietary name for carfentanil citrate marketed by Wildlife Laboratories, Incorporated. <https://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM473748.pdf>

⁽¹⁴⁾ A collected sample reported by Norway, where carfentanil was detected in a zip-lock bag containing powder, was labelled 'C.50'.

⁽¹⁵⁾ 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.

⁽¹⁶⁾ CAS RN 60645-15-0 is no longer in use by CAS for carfentanil although some vendors still reference this number.

⁽¹⁷⁾ InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

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

Physical description

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

Carfentanil is available as analytical reference material, reported as a pale yellow solid and which is soluble in chloroform (CHCl₃), dichloromethane (DCM) and ethyl acetate (18). Due to its similarity to fentanyl, the free base is expected to be sparingly soluble in water. The hydrochloride and citrate salts are expected to have greater aqueous solubility.

The measured melting point for carfentanil oxalate salt is 189.5°C (Van Daele et al., 1976) and 152.2°C for the citrate salt (Janssen and Van Daele, 1979).

Carfentanil is lipophilic.

Carfentanil has been seized in powder form and as a liquid. 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

Methods documented in the literature for the detection of carfentanil include: gas chromatography – mass spectrometry (GC-MS), Fourier transform infrared spectroscopy – attenuated total reflectance (FTIR-ATR) (Casale et al., 2017), nuclear magnetic resonance (NMR) (Casale et al., 2017, Malaquin et al., 2010) and by capillary electrophoresis coupled to electrospray ionisation tandem mass spectrometry (CE-ESI-MSⁿ, *n*=2,3), specifically non-aqueous capillary electrophoresis (NACE)-ESI-MSⁿ (Rittgen et al., 2012).

Methods have also been documented in the literature for the detection of carfentanil in biological samples, which include: high performance liquid chromatography – atmospheric-pressure ionisation – tandem mass spectrometry (HPLC-API-MS-MS) (Wang and Bernert, 2006), solid phase extraction (SPE) coupled with liquid chromatography – tandem mass spectrometry (LC-MS-MS) (Riches et al., 2012; Shaner et al., 2014) and ultra-high performance liquid chromatography ion trap mass spectrometry with MSⁿ capabilities (UHPLC-Ion Trap-MSⁿ) (Shoff et al., 2017).

The use of gas chromatography – flame ionisation detection (GC-FID) has been described for the quantitation of carfentanil in three illicit samples in the United States

(Casale et al., 2017). The samples were found to contain 0.62 %, 1.87 % and 0.31 % of carfentanil hydrochloride. Other substances detected in the samples, in trace amounts, included: diphenhydramine, fentanyl 2-furanylfentanyl and acetylcarfentanil. Carfentanil and acetylcarfentanil gave the same GC-MS retention time, however their mass spectra were different. The authors also reported that carfentanil citrate was easily differentiated from carfentanil hydrochloride when using NMR.

The implementation of chromatographic techniques, infrared and NMR spectrometry allow unambiguous differentiation between carfentanil and its two positional isomers, 2- and 3-carbomethoxyfentanyl. As of July 2017, detection of the positional isomers of carfentanil in Europe has not been reported to the EMCDDA.

Immunoassays developed for fentanyl are not necessarily expected to show cross-reactivity toward carfentanil (Mao et al., 2006). Commercially available immunoassays for carfentanil typically show cross-reactivity with sufentanil, alfentanil and remifentanyl but not with fentanyl (Ujváry, 2013).

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 18 Member States (Austria, Belgium, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, Poland, Romania, Slovakia, Slovenia, Sweden, and the United Kingdom) (19).

Five countries provided information on carfentanil (Finland, Germany, Lithuania, Sweden and the United Kingdom).

(18) <https://www.trc-canada.com/prod-img/MSDS/C183480MSDS.pdf>

(19) Canada also provided information to Europol on carfentanil.

The level of production

No information was received in relation to the production of carfentanil ⁽²⁰⁾.

The United Kingdom reported that there are indications that carfentanil has been shipped from predominantly China/Hong Kong and this has either been used as received, or mixed with other drugs, for example heroin, or cutting agents before being used or sold.

The level of distribution

At least 82 seizures were reported by five Member States: Finland (2), Germany (2), Lithuania (64), Sweden (4) and the United Kingdom (10) ⁽²¹⁾.

Finland reported 2 seizures of carfentanil, where the amounts were stated as minimal.

Germany reported 1 seizure of 99.3 g in 2016 by German customs and a seizure by Canadian law enforcement of approximately 62 g of 'suspected carfentanil' in June 2017. It was found in a package which was en-route from Hong Kong to Canada via Germany, using DHL. The seizure took place in Vancouver.

In 2017, Lithuania reported 25 seizures of carfentanil amounting to 264.777 g and 39 seizures of carfentanil amounting to 33.8 g which also contained heroin. The country of origin of the carfentanil in the seizures was unknown. Lithuania reported that seizures of carfentanil have increased in recent years. Carfentanil is often mixed with heroin and prepared for heroin users. Most cases are related to heroin distribution in the local Roma community.

Sweden reported 4 seizures of carfentanil made by the Swedish Police between the end of March and the end of April 2017. The amounts seized were reported as very small and that they were intended for end users. Two of the seizures were linked and were associated with cases that were suspected to involve deaths. In one case, it is known that the carfentanil was delivered in an envelope. They also stated that

⁽²⁰⁾ Canada reported that there is no evidence to date to indicate carfentanil production in the country. Carfentanil is sold as counterfeit oxycodone (CDN 80) or Xanax tablets. Carfentanil is imported in powder form and then tableted in the country.

⁽²¹⁾ Canada reported a total of 19 seizures, 10 of which occurred in 2016 and 9 in 2017. Seizures in 2016 amounted to 2.3 kg of powder and 6 pills. Six of the seizures were reported as importations seized at the Vancouver and at the Montreal international mail centres. The country of origin was reported as China (5 seizures) and Hong Kong (1). Seizures in 2017 occurred between January and mid-April and amounted to 258 g of powder (5 seizures) and 22 pills (1). The 5 seizures of powders were seized at the border (Vancouver international mail centre and FedEx in Memphis). The country of origin was reported as China (3 seizures), Hong Kong (1) and the United States (1). Canada also reported that powder fentanyl is often mixed with other illicit drugs such as heroin and cocaine. At street level, carfentanil is mostly found in tablet form. They noted that, in 2016, over 1 kg of carfentanil in powder form was seized imported into Quebec and an additional 1 kg was seized in Alberta.

carfentanil is ordered online from international (European) vendors and that there are no indications of domestic sale of the substance in Sweden.

The United Kingdom reported no seizures from January 2016 to March 2017. In April and May 2017, 10 seizures of carfentanil were seized that amounted to approximately 100 g. The biggest seizure was reported by Cleveland Police: 3 packages were seized amounting to 82 g and containing carfentanil, heroin, caffeine and paracetamol. Other substances detected in the seizures were: fentanyl (2); fentanyl, caffeine, and paracetamol (1); cocaine, caffeine, levamisole, phenacetin (1); and caffeine and paracetamol (2).

The National Crime Agency reported that they identified a supplier of carfentanil who was using the darknet to advertise and distribute carfentanil across the country and also internationally. A total of 19 customers in the United Kingdom are known to have purchased carfentanil from this site, placing a total of 37 orders. The size of orders varied from 50 mg (15 orders) to 1 g (1 order). It was also reported that there have been deaths associated with carfentanil, fentanyl, and fentanyl analogues since December 2016.

The level of trafficking

Information related to trafficking routes is limited to the seizures reported above. In cases where the country of origin was known, China and specifically Hong Kong were primarily reported with the United Kingdom and Germany also mentioned, but to a lesser extent ⁽²²⁾.

Lithuania reported that there are indications that carfentanil may be imported from Russia and China.

Information from ongoing investigations in Sweden indicates that carfentanil has been bought from internet vendors and delivered directly to the user (and/or to relatives of the user) from China, the United Kingdom and Germany. There are no indications that carfentanil is sold in Sweden.

Information from the United Kingdom indicates that carfentanil has been shipped from China/Hong Kong and the substance is either used as received, or mixed with other drugs, for example heroin, or cutting agents before being used or sold on.

3.2.2 Information provided to the EMCDDA

The EMCDDA received responses from the 28 Member States and Norway ⁽⁵⁾. Of these, 8 Member States and Norway

⁽²²⁾ Canada reported that carfentanil is imported in powder form and then tableted in the country.

reported detections of carfentanil ⁽²³⁾. Estonia, Germany, Finland, Latvia, Lithuania, Sweden and the United Kingdom reported seizures of carfentanil. In addition, Belgium, the United Kingdom and Norway reported collected samples.

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

Since 2016, there has been an increase in detections of carfentanil in Europe. The substance was initially detected in Latvia and Lithuania between 2012 and 2015. Subsequently, it then appeared in Estonia and Finland, and in the last 18 months or so it has been detected in a further five countries for the first time.

Seizures

In total, 755 seizures of carfentanil were reported to the EMCDDA by seven Member States: Estonia (116 cases), Germany (3), Finland (2), Latvia (387), Lithuania (233), Sweden (4) and the United Kingdom (10). The most recent reported detections were made in June this year, and at least 163 seizures reported for the first 6 months in 2017.

A large majority of the seizures were made by the police, with additional seizures taking place in custodial settings. Only one customs seizure was reported relating to 100 g seized at Cologne/Bonn airport in Germany.

Two Member States (Latvia and Lithuania) reported seizures from 2012 to 2015, as follows: 1 seizure in 2012 (Latvia), 27 seizures in 2013 (Latvia and Lithuania), 48 in 2014 (Latvia), and 160 in 2015 (Latvia and Lithuania). Latvia, Lithuania, Estonia and Finland reported 345 seizures in 2016 and Estonia, Germany, Finland, Latvia, Lithuania, Sweden and the United Kingdom reported 174 seizures in 2017.

The largest single seizure of carfentanil was reported by the United Kingdom. The seizure was made by West Yorkshire Police in May 2017, and amounted to 440 g of unadulterated carfentanil in powder form. In addition to this seizure, a total of six single seizures over 100 g were reported by four Member States as follows: Estonia (209.8 g, seized in April 2017), Germany (100 g reported through Police correspondence in 2017), Lithuania (2 seizures of 200 and 138.5 g, reported in

2016 and 2017) and the United Kingdom (2 seizures of 209 and 150 g).

Powders

Carfentanil was detected in powder form in a total of 618 cases: Estonia (110 cases), Germany (2), Finland (2), Latvia (383), Lithuania (108), Sweden (3) and the United Kingdom (10), amounting to nearly 2.7 kg of seized material. The quantification of carfentanil is not routinely performed; however, data on purity for 44 samples was reported by Lithuania.

In 187 of these seizures, carfentanil was the only substance reported.

In 278 seizures, carfentanil was detected in mixture with heroin. In addition to heroin, other substances detected were: cocaine, caffeine, paracetamol, levamisole and phenacetin (4 cases), methadone (3 cases), acryloylfentanyl (3), alpha-PHP (2) and caffeine and paracetamol (1).

In addition to the above substances, carfentanil has also been detected in mixtures with a number of other opioids. These include: fentanyl (81 cases), methadone (13), fentanyl and furanylfentanyl (10), fentanyl and acryloylfentanyl (7), furanylfentanyl (4), tramadol (3) and acryloylfentanyl (2).

Twelve seizures were reported of carfentanil mixed with the synthetic cathinone alpha-PHP.

Where reported, the powders were typically 'yellowish', both in cases where carfentanil was reported on its own and when mixed with heroin.

Liquids

Ten seizures of liquids were reported by Estonia (6), Latvia (3), and Sweden (1), amounting to a total of 1.75 g. All the seizures took place in 2017.

In 3 cases reported by Latvia, the liquids were found in syringes, of which two samples also contained alpha-PHP.

In 3 cases reported by Estonia, fentanyl was also detected in the liquid samples.

Other physical forms

The physical form was reported as 'other' for 75 cases, which were all reported by Latvia. These amounted to a total of 288.5 g and 0.67 ml of material seized. 47 of these samples also contained heroin.

No information on the physical form was reported for 52 cases, amounting to over 136 g and 0.5 ml of material seized.

⁽²³⁾ '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.).

Purity of carfentanil in seized samples

Information on the purity of carfentanil was provided for 44 samples reported by Lithuania. In 25 of the cases, heroin was also detected and the relative concentrations of both substances were provided.

The purity ranged from 0.00034 to 0.13 % carfentanil ⁽²⁴⁾ (mean: 0.043 %; median: 0.04 %). Thirty seven of the cases (86 %) were in the range of 0.03-0.09 % purity.

The concentration of heroin was reported for 63 samples and varied significantly between samples, ranging from 0.008 to 23.9 % pure heroin.

Collected samples

Four collected samples containing carfentanil, all in powder form, were reported to the EMCDDA by the United Kingdom (2 cases), Belgium (1) and Norway (1).

Both cases reported by the United Kingdom were samples submitted to the drug-checking service WEDINOS. Both samples were submitted as 'Fentanyl-HCL + Mannitol 15 % fentanyl', but carfentanil and mannitol were analytically detected instead.

The sample reported by Belgium was recovered from the scene of an apparent suicide, where a small quantity of powder collected, approximately 0.005 g, was found to contain carfentanil.

The sample reported by Norway also relates to a serious adverse event, where a powder was recovered from the scene of a death, found in a plastic bag labelled 'C.50'.

Biological samples

Serious adverse events with confirmed exposure to carfentanil from biological samples are discussed in section 3.4.2.

No other biological detections of carfentanil were reported to the EMCDDA.

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 the involvement of organised crime in the manufacture and/or trafficking of the carfentanil was provided ⁽²⁵⁾.

The United Kingdom reported that some online vendors of carfentanil have been identified as being run by more than one person; however there is little intelligence to confirm links to organised crime groups. Information suggests that carfentanil mixed with heroin was sold through travelling communities and networks in the North East of England, with this carfentanil possibly being supplied by one of these via online platforms/vendors.

In addition, the United Kingdom's National Crime Agency reported that they identified a supplier of carfentanil who was using the darknet to advertise and distribute carfentanil across the country and also internationally.

Money laundering aspects

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

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 carfentanil.

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 Health risks****Pharmacology and toxicology**

Carfentanil is a highly potent μ -opioid receptor agonist that acts as a narcotic analgesic (Bagley et al., 1991; Frost, 2001; Frost et al., 1989; Janssen, 1982; Van Bever et al., 1974; Van Bever et al., 1976).

⁽²⁴⁾ One very small sample was reported as 'pure' carfentanil, amounting to 0.00002 g. This was considered as an outlier and, therefore, it was not included in the calculation.

⁽²⁵⁾ Canada reported that they have not detected the involvement of organised crime groups, or that their involvement is limited. They reported that the darknet is often used to conduct transactions, which poses challenges in identifying the actors involved.

The effects of carfentanil share some similarities with other opioids such as morphine and fentanyl (Janssen, 1982; Janssen & Van der Eycken, 1968; Van Bever et al., 1974). In general, the acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, and respiratory depression (Dahan et al., 2001; Herz, 1993; Kieffer, 1999; Pasternak & Pan, 2013; Pattinson, 2008; Romberg et al., 2003). They also have an abuse liability and dependence potential.

Similar to other fentanils, the most serious acute health risk from using carfentanil is likely to be rapid and severe respiratory depression, which in overdose could lead to apnoea, respiratory arrest, and death (Dahan et al., 2010; EMCDDA, 2017; Lindsay et al., 2016; Pattinson, 2008; Wax et al., 2003; White and Irvine, 1999). Factors that may exacerbate this risk include: the difficulty in diluting the substance, which can lead to a toxic dose being inadvertently used; the use of routes of administration that have high bioavailability (such as injecting, insufflation, and inhalation); a lack of experience with its effects and dosing; the use of other central nervous system depressants at the same time (such as other opioids, benzodiazepines, gabapentanoids, and alcohol); no or limited tolerance to opioids; and, using the substance alone (such as at home) which would make it more difficult for users to call for help in the case of poisoning. In addition, as discussed below, as carfentanil is being sold as or in heroin and other illicit opioids, many users will not be aware that they are using carfentanil.

The antidote naloxone can reverse acute poisoning, including respiratory depression, caused by carfentanil (Kim and Nelson, 2015; Tiscione and Shanks, 2016; Lindsay, et al., 2016) ⁽²⁶⁾. Recent clinical and community experience in treating poisonings caused by fentanils suggests that higher doses and additional doses (including infusions) of naloxone may be required to fully reverse poisoning in some cases (CDC, 2013; FDA, 2016; Klar et al., 2016; Sutter et al., 2017).

The chronic health risks of carfentanil may share some similarities to opioids such as heroin and other fentanils. This is likely to include dependence (Aceto et al., 1988).

3.4.2 Serious adverse events

Acute intoxications reported to the EMCDDA

In total, three acute intoxications with confirmed exposure to carfentanil were reported by France (2 cases) and

Lithuania (1). The cases occurred in November 2016, January 2017, and May 2017 ⁽²⁷⁾.

The analytical detection of other substances was not reported. The clinical features of the intoxications were generally consistent with opioid toxicity.

The intoxications were considered life-threatening in at least two cases; all required hospitalisation of the patients. Naloxone was administered to the three patients; in at least two cases more than one dose was given to the patient. It was reported that naloxone was effective in one case; in another case, it was reported that 'several' doses of naloxone were not effective; the response to naloxone was not reported in the remaining case. All the patients survived.

In one case, the patient believed he was using cocaine and apparently snorted a powder containing carfentanil; in another, the patient reportedly tried a powder they had found at home; while in the remaining case, carfentanil was taken as a substance in its own right.

Deaths reported to the EMCDDA

In total, 48 deaths with confirmed exposure to carfentanil were reported by Belgium (1 case), Estonia (6), Finland (1), Lithuania (7), Norway (1), Sweden (3), and the United Kingdom (29) ⁽²⁸⁾. The cases occurred between November 2016 and the first half of 2017; at least 28 (57 %) of the deaths occurred in the United Kingdom between February and May 2017.

Where known, 29 were male (85 %) and five were female (15 %). The males were aged between 15 and 54 years (mean 37.8 years; median 39); the females were aged 21 to 36 years (mean 30.0; median 27).

A range of other substances were detected in the deaths. These were mostly other opioids (33 cases). Among the other opioids found, 6-monoacetylmorphine (6-MAM) and morphine (the two main active metabolites of heroin) were the most common detections (13 and 26 cases, respectively). Fentanyl and/or other fentanils were found in 22 cases ⁽²⁹⁾.

Where known, most of the individuals were found dead; in most cases this was in a home environment. In 21 cases, drug paraphernalia was found at or near the scene, including hypodermic syringes. In some cases the deceased was still

⁽²⁷⁾ In addition, France also reported an acute intoxication with suspected exposure to carfentanil. This case is not discussed further in this report.

⁽²⁸⁾ In total, 53 deaths were reported to the EMCDDA. Of these, 5 cases were excluded from the analysis because exposure to carfentanil had not been confirmed from biological samples taken from the patients.

⁽²⁹⁾ This included the detection of carfentanil, fentanyl and butyrfentanyl in 11 of the deaths reported by the United Kingdom.

⁽²⁶⁾ See also Wong et al., 2017.

holding the injecting equipment, suggesting that the death occurred suddenly.

In the majority of cases, the cause of death has not yet been reported as the deaths are still under investigation. In at least three cases, carfentanil caused or contributed to the death.

Additional information

Additional cases of acute intoxications ⁽³⁰⁾ and death investigations with confirmed exposure to carfentanil have been published in the scientific and medical literature (George et al., 2010; Müller et al., 2017; Seither and Reidy, 2017; Shanks and Behonick, 2017; Shoff et al., 2017; Sofalvi et al., 2017; Swanson, et al., 2017; Tiscione and Shanks, 2016).

3.4.3 Characteristics of users

Similar to other fentanils, carfentanil is sold and used as a 'legal' substitute for illicit opioids and prescription opioids; this may include for self-medication, such as the alleviation of pain and/or opioid withdrawal. In addition, carfentanil has also been sold as or in heroin in at least three Member States.

Data from law enforcement seizures and death investigations confirms that carfentanil is being used by high risk opioid users, including those who inject heroin and other illicit opioids. As carfentanil is being sold as or in heroin and other illicit opioids, most users will not be aware that they are using carfentanil. Other groups who may use carfentanil include those who are experimenting with the substance (such as psychonauts).

Evidence from Europe, the United States, and Canada shows that as well as being sold to users in or as heroin or other illicit opioids, fentanils such as carfentanil may also be sold as or in other illicit drugs such as cocaine, as well as used to make counterfeit medicines (such as opioid analgesics and benzodiazepines) (EMCDDA, 2017). As users will be unaware of this, it could increase the risk of severe and fatal poisoning in both opioid users and especially other user groups who may have no existing tolerance to opioids. Non-opioid users are unlikely to be aware of these risks and are unlikely to have access to community-based naloxone programmes, including take-home naloxone (EMCDDA, 2015; EMCDDA, 2016).

3.4.4 Social risks

While there is limited data for carfentanil, the social risks might share some similarities with other opioids such as heroin and other fentanils. Of particular note in this respect

is that carfentanil is being used by high risk opioid users, including those who inject heroin and other illicit opioids.

Similar to other fentanils, accidental exposure to carfentanil may also pose a risk of severe poisoning. Those at risk may include the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those working in the postal services and custodial settings (CDC, 2017).

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 23 May 2017, the World Health Organization informed the EMCDDA that carfentanil is currently not under assessment and has not been under assessment by the UN system.

Since then, the World Health Organization has published a list of substances that will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017. Carfentanil was included in the list of substances that will be reviewed. At the time of writing this report neither a critical review nor a written recommendation had been published.

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 carfentanil dates from 12 February 2013 from the Latvian national focal point. The Reporting Form details the seizure of carfentanil in 70.139 g of light yellow powder, seized by Latvian Police in Riga on 8 December 2012. The substance was analytically confirmed by GC-MS by the State Police forensic service department and by GC-MS and HPLC by the Latvian Institute of Organic Synthesis. Sugar was also detected in the sample.

Carfentanil was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through the European Union Early Warning System. A profile of the substance was created on the European Database

⁽³⁰⁾ These include some cases of suspected driving under the influence of drugs (Seither and Reidy, 2017; Tiscione and Shanks, 2016).

on New Drugs (EDND). Since then, analytical details and other information, including a public health alert, 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.

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)

Eleven Member States (Belgium, Cyprus, Czech Republic, Denmark, Estonia, Germany, Ireland, Latvia, Lithuania, Sweden, and the United Kingdom) and Norway reported that carfentanil is controlled under drug control legislation.

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

Finland reported that carfentanil is controlled under medicines legislation.

Thirteen Member States (Bulgaria, Croatia, France, Greece, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia and Spain) reported that carfentanil is not subject to control measures at the national level.

No response was received from Turkey ⁽⁵⁾.

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 or Norway, about the chemical precursors or manufacturing methods used to make the carfentanil which has been detected within Europe.

Carfentanil can be manufactured in illicit laboratories. Theoretically, it could be also sourced from the diversion of carfentanil intended to be used for veterinary medicine.

The synthesis of carfentanil has been described in the literature (Van Daele et al., 1976; Fraser-Reid and Taba, 1993; McClure et al., 1993). The synthesis of carfentanil is

considered to be more complicated than the synthesis for some other fentanyl derivatives.

The synthesis of carfentanil relies on *N*-phenylethylpiperidinone (NPP) as the starting material (Reiff and Sollman, 1992; Van Daele et al., 1976). The intermediate α -aminonitrile is obtained through the Strecker reaction of the aminoketone with potassium cyanide and aniline under acidic conditions. Partial hydrolysis of this nitrile produces the corresponding carboxamide, which, in turn, is converted into the methyl carboxylate. Carfentanil is produced following acylation of the resulting amino ester.

A method for the synthesis of carfentanil, which utilises the Ugi reaction has been reported in the literature (Malaquin et al., 2010). The authors report that this method is original, straightforward, rapid and efficient and that the Ugi reaction can be completed without obtaining side-products. They also report that this synthetic method for producing carfentanil is achieved in only two steps and produces a high yield, in comparison to other previously described methods.

Other high yielding methods have been described in the literature, which could be utilised in the clandestine manufacture of carfentanil (Marton et al., 2012; Butcher and Hurst, 2009; Reiff and Sollman, 1992; Taber and Rahimizadeh, 1992).

Two potential precursors of fentanyl and other fentanils, *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) as well as NPP (a pre-precursor), have been recently scheduled under the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988 ⁽³¹⁾.

The synthesis of carfentanil can be achieved using common laboratory equipment with commercially available glassware. The multi-step procedures described, require careful analysis and purification of the intermediates produced. The handling of the final product requires extreme caution to avoid potential absorption of the carfentanil-solution through the skin or the inadvertent inhalation of particles from the final product. Exposure of the skin and mucous membranes to fentanils, as well as their inhalation, poses a serious risk of accidental poisoning. In addition to exercising extreme caution, suitable personal protective equipment as well as sufficient stocks of naloxone as an antidote to poisoning following accidental exposure should be available when handling materials suspected to contain these substances (CDCP, 2013; US DEA, 2016).

⁽³¹⁾ Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.

In summary, the synthesis of carfentanil has been described in the literature. There is no information on the actual method(s) used for the production of carfentanil 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 carfentanil. 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 the Member States or Norway that indicated that carfentanil had any other use apart from in analytical reference materials and scientific research.

From the available information, it does not appear that carfentanil 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 database on the synthetic route of all medicinal products.

Twelve countries (Austria, Belgium, Croatia, Czech Republic, Finland, Germany, Greece, Latvia, the Netherlands, Slovenia, Spain and the United Kingdom) reported that carfentanil is not used to manufacture a medicinal product for human use. Four countries (Estonia, Hungary, Ireland and Sweden) reported that it was unknown if carfentanil is used to manufacture a medicinal product for human use.

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

Eleven countries (Austria, Belgium, Finland, France, Germany, Greece, Italy, Latvia, Poland, Slovakia and Spain) provided information that carfentanil is not used to manufacture a medicinal product for veterinary use. Six countries (Estonia, Ireland, the Netherlands, Portugal, Slovenia and Sweden) reported that it was unknown if carfentanil is used to manufacture a medicinal product for veterinary use.

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

In some countries, carfentanil is used in veterinary medicine for the immobilization and anesthesia of large animals (De Vos, 1978; Lian, 2016). For example, in the United States it is sold under the proprietary name Wildnil® (Wildlife Pharmaceuticals Incorporated, N.D.).

Radiolabelled carfentanil, ¹¹C-carfentanil, is used a positron emission tomography (PET) tracer in research studying the opioidergic system and drugs that act on that system (Frost, 2001; Piel et al., 2014).

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

Sixteen countries (Austria, Belgium, Croatia, Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Ireland, Latvia, the Netherlands, Slovenia, Spain, Sweden and the United Kingdom) reported that:

- carfentanil has not been granted a marketing authorisation as a medicinal product for human use;
- carfentanil is not the subject of an application for a marketing authorisation as a medicinal product for human use;
- there had been no cases of suspended marketing authorisation in respect to carfentanil as a human medicine.

Seventeen countries (Austria, Belgium, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Latvia, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain and Sweden) reported that:

- carfentanil has not been granted a marketing authorisation as a medicinal product for veterinary use;
- carfentanil is not the subject of an application for a marketing authorisation as a medicinal product for veterinary use;
- that there had been no cases of suspended marketing authorisation in respect to carfentanil as a veterinary medicine.

The EMA also reported that carfentanil:

- has not been granted a marketing authorisation as a medicinal product for neither human nor veterinary use through the centralised procedure;
- is not the subject of an application for a marketing authorisation for neither human nor veterinary use through the centralised procedure;
- is not the subject of a suspended marketing authorisation for neither human nor veterinary use through the centralised procedure.

5. Conclusion

Carfentanil belongs to a group of synthetic opioids known as the fentanils. It is closely related to fentanyl, which is controlled under the United Nations Single Convention on Narcotic Drugs, 1961. Carfentanil is likely to be a highly potent opioid narcotic analgesic in humans; as such, it is also likely to have an abuse liability and dependence potential. The most serious acute health risk posed by carfentanil is likely to be rapid and severe respiratory depression, which can be life-threatening. The antidote naloxone can reverse acute poisoning, including respiratory depression.

Carfentanil has been available in the European Union since at least December 2012. Since 2016, there has been an increase in the number of seizures reported. Typically it is seized as a powder, including in mixtures with heroin and other illicit opioids. To date, it has been detected in 8 Member States and Norway.

There are indications that at least some of the carfentanil currently available on the market is synthesised by chemical companies based in China. Carfentanil is sold both on the surface web and anonymous marketplaces on the darknet. It is available in wholesale amounts and in consumer amounts.

In total, 48 deaths with confirmed exposure to carfentanil have been reported by six Member States and Norway. Most of the deaths have occurred in the last six months. The majority of the deaths are still under investigation, however

in at least three cases, carfentanil was the cause of death or contributed to the death. Many of the decedents were high risk opioid users, including those who inject heroin and other illicit opioids.

Carfentanil is sold and used as a substitute for illicit opioids and prescription opioids. In at least three Member States, carfentanil has been sold as or in heroin. Similar to other fentanils, serious concerns exist that the substance could be supplied surreptitiously to a range of drug users. Most users are unlikely to be aware that they are using carfentanil.

From the available information in the European Union, it does not appear that carfentanil has been granted a marketing authorisation as a medicinal product for human or veterinary use; is the subject of an application for a marketing authorisation as a medicinal product for human or veterinary use; or that there had been cases of suspended marketing authorisation in respect to carfentanil as a human or veterinary medicine. Furthermore, from the available information it does not appear that carfentanil is used in the manufacture of a medicinal product in the European Union. However, the data collection from the Member States is incomplete.

Carfentanil is under assessment within the United Nations system. It will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017. Currently, neither a critical review nor a written recommendation has been published. Carfentanil is not subject to control measures in 13 Member States.

We conclude that the health and social risks caused by the manufacture, trafficking and use of carfentanil, 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.

The EMCDDA and Europol will continue to intensively monitor carfentanil 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.

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