CARFENTANIL

Critical Review Report

Agenda Item 4.8

Expert Committee on Drug Dependence

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Contents

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Summary

Carfentanil, a synthetic opioid agonist, is considered to be one of the most potent opioids known. It was developed by Janssen Pharmaceutica in 1974 and is an analog of the opioid analgesic fentanyl. It is estimated to be approximately 10,000 times more potent as an analgesic than morphine. Carfentanil is a controlled compound in 19 countries (Austria, Australia, Belgium, Canada, China, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Latvia, Lithuania, Poland, Sweden, the United Kingdom, and the United States) and is used primarily as a tranquilizer in large animals. It is not intended for therapeutic use in humans, although it has been used widely in the scientific community as a radiotracer in positron emission tomography (PET) imaging studies in both humans and laboratory animals.

Receptor binding studies have shown that carfentanil binds selectively and competitively to the μ subtype of opioid receptors relative to δ and κ opioid receptors. Preclinical studies have demonstrated that the pharmacodynamic effects, such as analgesia and constipation, produced by carfentanil are similar to other μ opioid agonists. Its extreme potency and propensity to produce rapid and profound respiratory depression has prompted recommendations that an opioid antagonist, such as naloxone or naltrexone, be available whenever carfentanil is used or suspected to be present.

No controlled laboratory studies have evaluated the abuse potential of carfentanil in any species. However, several reports of illicit carfentanil seizures have appeared around the world over the past few years. It is typically added to or sold as heroin or prescription pills on the illicit market, often unbeknownst to the user. Reports of carfentanil-laced cocaine are also now appearing in the United States.

Reports of fatal overdoses involving carfentanil are increasing substantially, in part due to the availability of methods to detect carfentanil in body fluids. Carfentanil poses a serious threat to the public health.

1. Substance identification

A. International non-proprietary name (INN)

Carfentanil

B. Chemical Abstract Service (CAS) registry number

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

C. Other names

1. (4-methoxycarbonyl)fentanyl
2. ^{11}C-carfentanil
3. 4-methoxycarbonyl fentanyl
4. 4-methoxycarbonylfentanyl
5. carfentanil citrate
6. carfentanil oxalate
7. carfentanil, (+-)-isomer
8. carfentanyl
9. R 31833
10. R 33799
11. R-31833
12. R31833
13. NIH 10570
14. Carfentanila [INN-Spanish]
15. Carfentanilum [INN-Latin]
16. Wildnil
17. 59708-52-0
18. UNII-LA9DTA2L8F
19. Methyl 1-phenylethyl-4-(N-phenylpropionamido)isonipecotate
20. CHEBI:61084
21. Methyl 4-(N-(1-oxopropyl)-N-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylate
22. Methyl 4-(N-propionyl-N-phenylamino)-1-(2-phenylethyl)-4-piperidine-carboxylate
23. 4-((1-Oxopropyl)phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid methyl ester
24. LA9DTA2L8F
25. R-33799
26. BRN 0456976
27. CHEMBL290429
28. methyl 1-(2-phenylethyl)-4-(N-propanoylanilino)piperidine-4-carboxylate
29. methyl 1-(2-phenylethyl)-4-[phenyl(propionyl)amino]-4-piperidinecarboxylate
30. methyl 1-(2-phenylethyl)-4-[phenyl(propionyl)amino]piperidine-4-carboxylate
31. methyl 1-phenethyl-4-(N-phenylpropionamido)piperidine-4-carboxylate
32. methyl 1-phenylethyl-4-(N-phenylpropionamido)isonipecotate
33. methyl 4-[phenyl(propanoyl)amino]-1-(2-phenylethyl)piperidine-4-carboxylate

34. methyl 4-[(1-oxopropyl)phenylamino]-1-(2-phenylethyl)-4-piperidinecarboxylate
35. 1-phenethyl-4-(N-propionyl-anilino)-piperidine-4-carboxylic acid methyl ester
36. 4-[(1-oxopropyl)phenylamino]-1-(2-phenylethyl)-4-piperidinecarboxylic acid methyl ester
37. 4-carbomethoxyfentanyl
38. 3-demethyllofentanil

D. Trade names

WildNil (carfentanil citrate) was marketed by Wildlife Laboratories, Inc. as a prescription-only general anesthetic for intramuscular injection in large animals. It is now only available as a compounded medication in a concentration of 3 mg/mL in a 10 mL vial.

E. Street names

Carfentanil is known as "elephant tranquilizer" (Ohio Substance Abuse Monitoring Network, March 2017) and "C.50". It also can be an active ingredient of the street drug "gray death" in combination with heroin, fentanyl, and the synthetic opioid U-47700. Newspapers have reported that street names for carfentanil and fentanyl may be "drop dead" and "serial killer".

F. Physical properties

Carfentanil is a white granular or crystalline powder. As analytical reference material, it is a pale yellow solid that is soluble in chloroform ($CHCl_3$), dichloromethane (DCM), and ethyl acetate. "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" (EMCDDA-Europol Joint Report, 2017).

G. WHO review history

Carfentanil has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that carfentanil is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

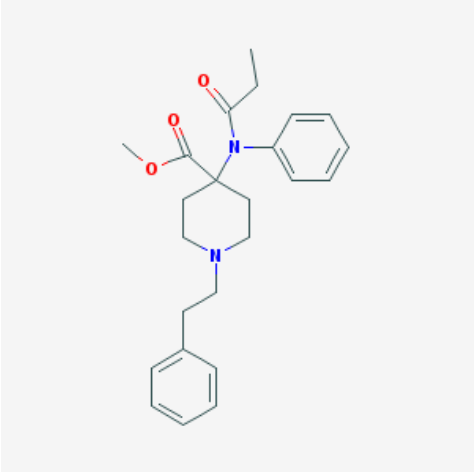
2. Chemistry

A. Chemical name

IUPAC name: Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate
CA index name: 4-Piperidinecarboxylic acid,4-[(1-oxopropyl)phenylamino]-1-(2-phenylethyl)-,methyl ester

B. Chemical structure

Free base:



Molecular Formula: $C_{24}H_{30}N_2O_3$
Molecular Weight: 394.515 g/mol
Melting point: 189.5 ºC (oxalate salt; van Daele et al., 1976)
152.2 ºC (citrate salt; van Daele et al., 1976)
Boiling point: 508.1ºC at 760 mmHg

C. Stereoisomers

None.

D. Methods and Ease of Illicit Manufacturing

Carfentanil was first synthesized in 1974 by a team of chemists, including Paul Janssen, at Janssen Pharmaceutica (van Daele et al., 1976). Various strategies for synthesizing carfentanil have been reported in the literature (e.g., Janssens et al., 1986; van der Heijden et al. 2016; Váradi et al. 2015; and Vardanyan and Hruby 2014). For example, 4-arylamino-4-piperdinecarboxylic acids can be used as starting materials to produce carfentanil and other strong analgesics through variations of the Strecker reaction (Vardanyan and Hruby 2014). A key ingredient in the illicit synthesis of carfentanil is *N*-phenethyl-4-piperadone (NPP), which can be purchased at low cost. Through a 3-step process involving 1. Potassium cyanide, aniline, acid; 2. Methanol, acid; and 3. Propanoyl chloride, carfentanil can be produced. “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), NPP have been recently scheduled under the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.” (EMCDDA-Europol Joint Report, 2017).

“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." (EMCDDA-Europol Joint Report, 2017).

E. Chemical properties

Carfentanil is comprised of a carboxymethyl group in the fourth position of the piperidine ring of fentanyl. Carfentanil solution is a clear, highly water soluble liquid with no distinguishing odor (George et al., 2010). Its high lipophilicity, which allows greater penetration of the blood-brain barrier, is thought to contribute to its high potency.

F. Identification and Analysis

Carfentanil belongs to the 4-anilidopiperidine class of synthetic opioid analgesics that includes fentanyl, sufentanil, alfentanil, and remifentanil. Carfentanil can be detected in the whole blood, post-mortem blood, and urine, but only a limited number of labs are able to test for carfentanil or have reference materials to identify it (Randox Toxicology, 2017). Standard urine drug tests will not detect carfentanil. A one-step testing kit for carfentanil is marketed for forensic purposes by Neogen Corporation (LOQ: 0.1 ng/mL). Source: http://toxicology.neogen.com/en/carfentanil-forensic

It has been noted that carfentanil is difficult to detect using general GC/MS screening methods due to its potency (Swanson et al., 2017). Because more sensitive instrumentation such as LC–MS-MS is typically not performed, it is possible that the rate of carfentanil-related incidents is underestimated due to lack of detection. In Miami-Dade County, carfentanil was initially missed in 104 of the 134 cases (using GC/MS), until a more sensitive method (LC-Ion Trap MSn) was used and facilitated detection.

Available methods for detecting carfentanil were summarized by the EMCDDA-Europol Joint Report (2017): "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 eclectrophoresis 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 crossreactivity toward carfentanil (Mao et al., 2006). Commercially available immunoassays for carfentanil typically show cross-reactivity with sufentanil, alfenantil and remifentanyl but not with fentanyl (Ujváry, 2013)."

3. Ease of convertibility into controlled substances

Sufentanil and alfentanil, two potent FDA-approved opioid analgesics which are listed in Schedule 1 of the 1961 Convention on Narcotic Drugs, can be produced by two small changes in the carfentanil structure (e.g., "reduction of carbonyl group in carboxy-function in the fourth position of piperidine ring transforming it to a methoxymethylene group and isosteric replacement of the phenyl ring at the phenethyl group with an heteroaromatic thienyl- and tetrazolyl rings" (Vardanyan and Hruby, 2014)).

4. General pharmacology

Carfentanil binds competitively to μ opioid receptors, with subnanomolar affinity (0.1 nM) and an *in vitro* K_D of 0.08 nM in human and rat brain (Titeler et al., 1989). It also binds competitively to κ and δ opioid receptors. In rat brain tissue homogenates, carfentanil was equipotent in displacing the μ and κ radioligands and less potent in displacing the δ ligand. The relative selectivity for μ/κ/δ was reported to be 1:1:1666 for the high affinity sites and 1:1.5:445 for the low affinity sites (Thompson et al., 1987). A binding study in rat brain showed that [^{11}C]carfentanil had a higher affinity and binding potential for μ_1 compared to μ_2 receptors (Eriksson and Antoni, 2015). The Ki values of carfentanil for human opioid receptors were 0.024 nM μ_1), 3.3 nM (δ), and 43 nM (κ), and the rank order of potency was μ>>>δ>κ (Zawilska, 2017).

A. Routes of administration and dosage

Fentanyl-related substances, including carfentanil, have been identified in powder, tablet, or capsule formulations as well as in liquid form and on blotter paper (DEA, 2017). Thus, it can be pharmacologically active via multiple routes of administration, including orally, intranasally, subcutaneously, intravenously, and intramuscularly.

The preferred route of administration to anesthetize large animals is intramuscularly via a dart, in doses ranging between 0.005 and 0.020 milligrams per kilogram of body weight. Due to its high potency, carfentanil also can be easily absorbed through the skin or inhaled (Swanson et al., 2017). As a result, it is recommended that extreme caution and protective equipment be used by persons who may be exposed to carfentanil (Lust et al., 2011).

According to the EMCDDA (2017), carfentanil has been 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. Ten seizures of liquids were reported by Estonia (6), Latvia (3), and Sweden (1), amounting to a total of 1.75 grams. 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. (EMCDDA-Europol Joint Report, 2017).

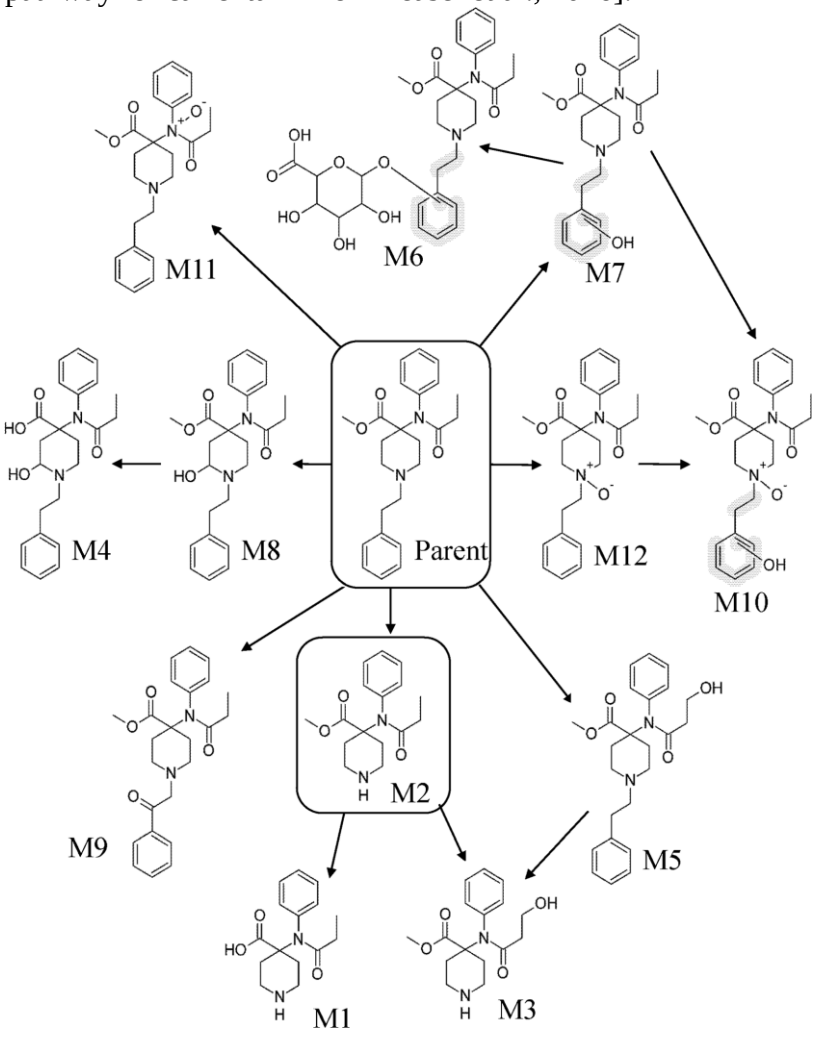
B. Pharmacokinetics

Limited pharmacokinetic information is available on carfentanil in non-human animals (Cole et al., 2006; Mutlow et al., 2004) and humans (Minkowski et al., 2012). The first report on carfentanil pharmacokinetics for any species was published in 2004 (Mutlow et al., 2004). In the domestic goat (*Capra hircus*; n=8), intramuscular administration of carfentanil (dose: 40 μg/kg) led to rapid absorption, with time to maximum effect (T_{max}) at 11 min (Mutlow et al., 2004). Plasma concentrations subsequently declined in a biphasic pattern. The effects of carfentanil were long lasting, with a half-life ($t_{1/2}$) of 5.5 hours. Carfentanil plasma concentrations (LOQ: 0.0085 ng/ml) could be detected in all goats for at least 12 hours.

In the adult female common eland (n=6; Cole et al., 2006), carfentanil was rapidly absorbed following intramuscular administration (0.0169 0.0005 mg/kg), with peak plasma concentration T_{max} at 14 min. However, the first blood sample post-dosing was drawn at 10 minutes, and it is thus possible that individual T_{max} values for individual animals may have occurred at less than 10 minutes post-dosing. There was a sharp decline in plasma concentrations over the next 12 hours, but plasma carfentanil remained detectable (LOQ: 0.0085 ng/ml) in all six of the animals for at least 32 hours. The mean t½ was 7.7 hours.

Lust et al. (2011) reported that "Carfentanil has rapid onset [following IM administration] in animal patients, and is metabolized by the liver and excreted in the bile or by the kidneys (3)."

Feasel et al. (2016) identified a total of twelve metabolites by incubating carfentanil with human hepatocytes *in vitro*: "N-Dealkylation and monohydroxylation of the piperidine ring were the dominant metabolic pathways. Two N-oxide metabolites and one glucuronide metabolite were observed. Surprisingly, ester hydrolysis was not a major metabolic pathway for carfentanil. While the human liver microsomal system demonstrated rapid clearance by CYP enzymes, the hepatocyte incubations showed much slower clearance, possibly providing some insight into the long duration of carfentanil's effects." [See figure below of the proposed metabolic pathway for carfentanil from Feasel et al., 2016].



The metabolite norcarfentanil may also be associated with carfentanil, based on a urine sample collected from an individual who had been exposed to a combination of carfentanil and remifentanil (Riches et al., 2012).

In healthy human volunteers (n=13), the $t_{1/2}$ of carfentanil was 42 minutes (SD: 18 minutes) following bolus IV administration (dose: 0.019 µg/kg; Minkowski et al., 2012).

C. Pharmacodynamics

Carfentanil exerts its principal pharmacologic effects on the central nervous system, although its anti-diarrheal effects are most likely produced peripherally. Similar to other µ opioid agonists, it depresses the respiratory center, suppresses the cough reflex, and causes pupil constriction. It also induces side effects such as drowsiness and sedation. Although it can produce analgesic effects (Stahl et al., 1977), carfentanil is used primarily in veterinary medicine as a tranquilizer because of its high potency and rapid onset of sedating effects. For example, in mice exposed to aerosolized carfentanil, loss of consciousness was observed within 1 min (Wong et al., 2017). In domestic goats, an intramuscular dose of 40 mg/kg made the animals recumbent within 84 ± 18 sec post-dose (Mutlow et al., 2004). The pharmacodynamic effects of carfentanil can be reversed by opioid antagonists, such as naloxone and naltrexone (Lust et al., 2011): "Naloxone (Narcan®; Bristol-Myers Squibb, New York, NY) is the opioid antagonist used for the reversal of carfentanil and is the preferred treatment in human health care settings (3,4). However, veterinary practitioners exposed in the field may self-administer the veterinary-labeled naltrexone 50 mg/mL concentration that is made via the same compounding pharmacy source. It is important to note that this medication is not intended for human use, but given the severity of carfentanil exposure, using what is immediately available may be acceptable in a life-or-death situation. Such use of naltrexone is limited to remote exposures outside of a hospital environment when time constraints preclude waiting for emergency medical care. The compounded veterinary naltrexone is acquired from the same compounding source as carfentanil and is used to reverse the effects of carfentanil in the field in animal patients (4). The recommended dose for animal reversal is a ratio of 100 mg of naltrexone for every 1 mg of carfentanil delivered (4)."

Although no controlled studies have examined the doses of naloxone or naltrexone needed to reverse the effects carfentanil, a study conducted in rats demonstrated that naltrexone was equipotent in antagonizing the analgesic effects of fentanyl and morphine (Comer et al., 1992).

5. Toxicology

The toxic or lethal human dose of carfentanil is unknown. Due to the high potency of carfentanil, the DEA recommends that naloxone be available to administer in case of accidental carfentanil exposure (DEA, 2016). The following studies have reported or discussed the toxic effects of carfentanil:

- In rats, the LD_{50} (lethal dose in 50% of the animals tested) of carfentanil was 3.39 mg/kg after intravenous administration (van Bever et al., 1976).
- George et al. (2010) presented the first case report of human carfentanil poisoning: A 42-year old veterinarian was splashed in the eyes and mouth with a dart containing

1.5 mg carfentanil citrate and 50 mg xylazine hydrochloride, intended for the sedation of elk. Onset of symptoms (drowsiness) occurred within 2 minutes of exposure. The veterinarian fully recovered after receiving 100 mg oral naltrexone.

- Carfentanil and remifentanil were detected on clothing and in a urine sample from survivors of a Moscow theatre siege (Riches et al., 2012). In that event, Chechen terrorists seized a theatre and took over 800 hostages. After days of unsuccessful negotiations, Russian military personnel pumped a chemical aerosol into the building through the ventilation system and then raided it. Approximately 33 terrorists and 129 hostages died during or shortly after the raid. "The Russian Government (5) commented that hospital care for those most intoxicated involved oxygen administration, mechanical ventilation and injection of naloxone. Less affected individuals were torpid, disoriented and vomiting, had pinpoint pupils, bradycardia and hypotension, and received symptomatic treatment." (Riches et al., 2012).
- Swanson et al. (2017) noted: "While there are no known publications on carfentanil human toxicity, expected symptoms are consistent with opioid toxicity which includes sedation, dizziness and [potentially life-threatening] respiratory depression. Naloxone can reverse these effects although several doses of naloxone may be required due to the unusually high potency of carfentanil (DEA, 2016; Lust et al., 2011)."
- Lust et al. (2011): "The human health hazard with regard to carfentanil is related to the potency of the medication. Exposure to the medication typically would be accidental via occupational use. Toxic exposure can occur through accidental injection with a syringe or dart, by absorption through mucus membranes (eyes, nose, mouth) or by direct absorption through broken skin."
- A literature review of deaths involving fentanyl and its analogs revealed that the majority of deaths was associated with pulmonary edema and congestion, as well as aspiration of gastric contents (Giorgetti et al., 2017). Cardiac and liver abnormalities (organomegaly, fatty infiltration, or fibrosis) were also reported.
- Carfentanil has been detected in overdose deaths in Ohio and Florida (CDC, 2016). In Hamilton County, OH, carfentanil accounted for at least 8 overdose deaths between July and September 2016 (WLWT, 2016). In Hillsborough County, Florida, where deaths from fentanyl and fentanyl analogs increased by more than twofold between 2014-16, two overdose deaths were reported in 2016 where carfentanil was identified and ruled to be the cause of death, either alone or in combination with other drugs (see Swanson et al., 2017 for case reports).
- In Miami-Dade County, carfentanil was detected in 134 overdose deaths starting in July 2016 (Shoff et al., 2017). Shoff et al. (2017) note that carfentanil "has contributed immensely to the nationwide opioid epidemic with reports of accidental overdoses surfacing from coast to coast", but the incidence rate of carfentanil overdoses is not clear. Toxicology examinations for suspected opioid overdose deaths do not routinely test for carfentanil and other emerging fentanyl analogs (CDC, 2017).

In the EMCDDA-Europol Joint report (2017) it is stated that "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. 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. 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." (EMCDDA-Europol Joint Report, 2017).

In the EMCDDA-Europol Joint Report a total of 3 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 2 cases; all required hospitalization of the patients. Naloxone was administered to 3 of the patients; in at least 2 cases more than one dose was given to the patient. It was reported that naloxone was effective in 1 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. Also 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." (EMCDDA-Europol Joint Report, 2017).

6. Adverse reactions

Non-human animals:

- Cole et al. (2006): "The side effects of carfentanil include hyperexcitation upon administration, potentially leading to hyperthermia and exertional myopathy; regurgitation; severe respiratory depression; muscular tremors; tachycardia; and renarcotization (20). Renarcotization is the reoccurrence of the opioid-agonist effects up to 72 hr after apparent anesthetic recovery (11). It varies in severity from mild sedation to full immobilization, and has been associated with an increased incidence of mortality (2,12,16,18). The choice of antagonist dose is an important factor in the probability of renarcotization (1,2,12,18). Additionally, certain species appear to have a higher likelihood of renarcotization than others (1), yet the predisposing factors that contribute to renarcotization among nondomestic animals are currently unknown. Possible mechanisms of renarcotization have been described and include metabolism of the antagonist to form a metabolite with agonistic properties, release of the agonist from body depots after the antagonist has been eliminated, antagonist underdosing, and metabolism of a short-acting antagonist with reestablishment of a longer-acting agonist (11). Hypothetically, the use of a long-acting opioid antagonist should prevent or decrease the incidence of renarcotization following carfentanil immobilization (18). Naltrexone hydrochloride has become the antagonist of choice for reversal of

carfentanil immobilization. This is because of the belief (with no definitive data in use species) that naltrexone has a longer half-life than other opioid antagonists and that the incidence of renarcotization is low with its use (18,25,28,29)."

Humans:

- In healthy non-drug-using volunteers (n=15) participating in a PET imaging study, a 0.019 μg/kg dose of [^{11}C]-carfentanil given as an intravenous bolus produced self-reported adverse effects in 60% of subjects, with dizziness (60%) and nausea (33%) being the most common symptoms, followed by vomiting and itching (both 7%; Minkowski et al., 2012).
- Lust et al. (2011): "Signs and symptoms of exposure [to carfentanil] are consistent with opioid toxicity and include pinpoint pupils, respiratory depression, and depressed mental status. Other signs and symptoms include dizziness, lethargy, sedation, nausea, vomiting, shallow or absent breathing, cold clammy skin, weak pulse, loss of consciousness, and cardiovascular collapse secondary to hypoxia and death."
- EMCDDA (2015): "Serious interactions can occur when fentanyls are mixed with heroin, cocaine, alcohol and other CNS depressants e.g. benzodiazepines."
- In a survey of 64 drug users who were trained to recognize the signs and symptoms of opioid overdose and how to use naloxone to reverse an opioid overdose, respondents indicated that suspected fentanyl overdoses were characterized by rapid onset ("within seconds to minutes") and "immediate blue discoloration of the lips (20%), gurgling sounds with breathing (16%), stiffening of the body or seizure-like activity (13%), foaming at the mouth (6%), and confusion or strange affect before unresponsiveness" (Somerville et al., 2017). Furthermore, a majority of respondents indicated that 2 or more doses of naloxone were required to reverse a suspected fentanyl overdose (typically administered nasally at a concentration of 2mg/2ml). Carfentanil was not specifically examined in this study, however.

7. Dependence potential

Controlled pharmacology data on the dependence or tolerance potential of carfentanil in non-human species and humans are unavailable.

8. Abuse potential

The abuse potential of carfentanil has not been tested in controlled studies in either preclinical or clinical research.

EMCDDA (2015): "[While] carfentanil is said to be 10,000 times more potent than morphine, it is difficult to be certain that this increased analgesic potency means that the euphoric effects are similarly increased, and more importantly, whether the overdose potential of these analogues is also increased by the same margin".

Euphoria is considered to be less pronounced with the fentanyls than with heroin and morphine (EMCDDA, 2015). However, controlled laboratory studies in humans to assess the abuse liability of fentanyl have shown that they produce a profile of subjective effects in opioid abusers that is similar to other mu opioid agonists, including heroin and structurally similar drugs, such as alfentanil (Comer, et al., 2008; Greenwald, et al., 1996). In normal,

healthy volunteers with little or no experience with opioids, however, fentanyl produces equivocal effects on measures of euphoria (Zacny et al., 1992a, 1992b, and 1996).

9. Therapeutic applications and epidemiology of medical use

Carfentanil was first synthesized in 1974 by Janssen Pharmaceutica and introduced in veterinary medicine in 1986 (Stanley et al., 2008). It is primarily used as an anesthetic agent for large animals.

[^{11}C]-carfentanil was first used in 1985 as a PET radiotracer (Colasanti et al., 2013) and has been an important research tool to evaluate μ opioid receptor function in various populations, including those with alcohol, cocaine, nicotine, and opioid use disorders, as well as chronic pain (Ghitza, 2014).

10. Listing on the WHO model list of essential medicines

Carfentanil is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing authorizations (as a medicine)

There are no marketing authorizations as a medicine for carfentanil for use in humans. In veterinary practice, Wildnil (carfentanil citrate), sponsored by Wildlife Laboratories, Inc. (Lowell, AR), was licensed as a prescription-only drug for use as an "immobilizing agent in free-ranging or confined members of the family Cervidae (deer, elk, moose)" (see FDA file number: NADA 139-633). However, "commercial production of Wildnil ceased in 2003, and the drug is available only as a compounded dosage form in a concentration of 3 mg/mL, in 10-mL vials" (Lust et al., 2011).

12. Industrial use

Small quantities of carfentanil are imported for use as an analytical reference standard.

13. Non-medical use, abuse, and dependence

Carfentanil is not mentioned in the 2015 SAMHSA's annual National Survey on Drug Use and Health (NSDUH) and the 2017 Global Drug Survey provides no information on prevalence of use. No controlled studies of the non-medical use, abuse, or dependence potential of carfentanil have been performed.

Opioid users who suspect that they have used fentanyl report that compared to heroin, fentanyl produces a "more intense 'rush' (i.e. explosive onset of strong opioid effect), greater potency and a shorter duration of effect" (Ciccarone et al., 2017). However, other users report a less desirable "high" than other mu agonists (i.e., it is described as "a mucky, dirty feeling almost" and other adverse effects are reported such as "a "flushing" effect in the face, shortness of breath, blurry vision and skin tingling," "sudden respiratory effects," and "seizure symptoms"; Ciccarone et al., 2017). Because other substances are often added

to illicit fentanyl (including carfentanil), it is impossible to know whether these adverse effects are due to fentanyl per se or adulterants in the fentanyl.
Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Public health problems related to misuse, abuse, and dependence

In Europe, the first reports of carfentanil seizures occurred in December 2012 in Latvia and it was reportedly linked to a spate of deaths among injecting drug users in the country the following year (EMCDDA, 2014). High mortality rates related to the fentanyls have continuously been reported in Estonia since the mid-2000s. In Germany, Finland and the United Kingdom reported individual outbreaks of fentanyl-related deaths in the early 2010s (Mounteney et al., 2015), but it is unknown whether carfentanil was present.

There have been several media reports suggesting that carfentanil is being taken with heroin or by users who are taking heroin. Carfentanil is added to or sold as heroin because it's less expensive, easier to get (Chinese firms advertise and sell carfentanil over the Internet, offering advice to customers in other countries on how to import it illegally) and easier to make than genuine heroin. There also have been several news articles in the United Kingdom, United States and other countries suggesting that carfentanil has been involved in overdoses and fatalities.

In 2016, the Kentucky State Police reported carfentanil submissions from 10 Kentucky counties (Appendix, Fig. 2); 9 carfentanil overdose deaths have been identified so far in preliminary 2016 DC data; 6 of the decedents resided in counties with reported carfentanil seizures." (Slavova et al., 2017).

Laboratory testing of urine samples from drug users in British Columbia, Canada between January 10-24, 2017 detected the presence of carfentanil in 57 of 1766 samples. Positive results were detected in samples originating from treatment facilities in Vancouver, Surrey, New Westminster, Maple Ridge, and Richmond [1]

EMCDDA (2015): "In the case of non-pharmaceutical fentanyls, many deaths — characterised by their suddenness — have been caused by the use of heroin laced with fentanyl or with one of its more potent analogues."

In the United States, the DEA (2017) stated that: According to Centre for Disease Control data, 9,580 opioid overdose deaths in 2015were caused by synthetic opioids other than methadone, which includes fentanyl and fentanyl-related substances - an increase of 72.2 percent over previous years. The DEA Special Testing and Research Laboratory's Emerging Trends Program also reported that during the second quarter of 2017, there were 269 identifications of "fentanyl, fentanyl-related substances, and other synthetic opioids." Fentanyl accounted for 69% of the identifications (187 out of 269) and carfentanil accounted for 3.3% of the identifications (9 out of 269). Other controlled substances identified with fentanyl this quarter included cocaine, tramadol, U-47700, ketamine, and other fentanyl-related compounds.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

[1] *https://news.gov.bc.ca/releases/2017HLTH0020-000224*

15. Licit production, consumption, and international trade

Prior to the addition of carfentanil to the list of controlled substances in China (effective March 1, 2017), it could be manufactured legally in China. It was actively marketed by several Chinese chemical companies and sold to the United States, Canada, the United Kingdom, France, Germany, Belgium and Australia for as little as $2,750/kg, "no questions asked" (AP, 2016).

16. Illicit manufacture and traffic and related information

In Europe, carfentanil seizures were first reported in December 2012 in Latvia (EMCDDA, 2014). Subsequently, neighboring Lithuania reported further seizures of carfentanil by police in February 2013 in Vilnius (Mounteney et al., 2015). In Finland, first seizures of carfentanil were reported by Finnish customs in July 2017, following earlier carfentanil seizures in Sweden, Belgium, Estonia and the UK (Finnish Customs, 2017). In Australia, the first carfentanil seizure was reported by the Australian Border Force in Sydney in December 2016.

As reported by the EMCDDA-Europol Joint report on carfentanil (2017): The U.K. reports that carfentanil is primarily shipped from China/Hong Kong, where it has been "used as received, or mixed with other drugs, for example heroin, or cutting agents before being used or sold." Furthermore, Finland, Germany, Lithuania, Sweden and the U.K. reported seizures of carfentanil ranging from "very small" amounts to 100 g.

Carfentanil and other illicit fentanyl forms, both imported and clandestinely manufactured have been shipped via mail services from China to Canada, the U.S., and Mexico, where they are used as adulterants in other controlled substances such as heroin, cocaine, and methamphetamine. (DEA, 2017; Shoff et al., 2017). In August 2016, Canadian authorities in Vancouver announced that they had seized a shipment from China containing one kilogram, or 50 million lethal doses, of carfentanil (Gussow, 2016).[2] .] An additional one kilogram of carfentanil was seized in Alberta (EMCDDA-Europol Joint Report, 2017). "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." (EMCDDA-Europol Joint Report, 2017). It is unclear to what extent carfentanil continues to be manufactured in China, where it was rescheduled on March 1, 2017 and is now a controlled substance.

The EMCDDA-Europol Joint Report (2017) states that "In February of 2017, a series of carfentanil listings on the AlphaBay cryptomarket were the subject of heated online debate about the ethical and logistical implications of prohibiting such products to be offered (14Handbottles; SecondChanceUsername, 2017). Those discussions resulted in the removal of carfentanil listings by that vendor, apparently in response to community dissent." (Gilbert and Dasgupta, 2017). The typical cryptomarket process is as follows: 1) Buyer places order with Market (after browsing and searching the marketplace using an Internet traffic-

[2] *http://journals.lww.com/em-news/Fulltext/2016/11000/Toxicology_Rounds__Who_Said_the_Opioid_Crisis.5.aspx*

obfuscating browser, such as Tor), 2) Buyer sends Bitcoin to Market escrows, 3) Vendor gets order and escrow confirmation, 4) Vendor ships product, 5) Buyer confirms receipt, 6) Market releases escrow to Vendor, and 7) Buyer leaves feedback on Market (Gilbert and Dasgupta, 2017). In terms of trafficking routes, "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" (EMCDDA-Europol Joint Report, 2017).

17. Current international controls and their impact

Carfentanil is not controlled under the 1961 UN Single Convention on Narcotic Drugs (EMCDDA, 2015) or the 1971 United Nations Convention on Psychotropic Substances.

18. Current and past national controls

The U.S. Drug Enforcement Agency placed carfentanil in Schedule II of the Controlled Substances Act (CSA) on October 28, 1988. Carfentanil has a DEA ACSCN of 9743 and a 2016 annual aggregate manufacturing quota of 19 g ("Established Aggregate Production Quotas for Schedule I and II Controlled Substances and Assessment of Annual Needs for the List I Chemicals Ephedrine, Pseudoephedrine, and Phenylpropanolamine for 2016". Federal Register. 6 October 2015.) The U.S. Department of Defense considers carfentanil a dangerous weapon, and the substance is banned from the battlefield under the Chemical Weapons Convention.

In Australia, carfentanil is scheduled as S8 (Controlled). In Canada, carfentanil is a controlled Schedule I drug. In China, the National Narcotics Control Commission added carfentanil to its list of controlled substances effective March 1, 2017. In Germany, carfentanil is classified as a narcotic (Betaeubungsmittelgesetz, Anlage I) and is only authorized for scientific use. In the UK, carfentanil is classified as Class A substance (Schedule 2) under both the Misuse of Drugs Act 1971 (MDA) and the Misuse of Drugs Regulations 2001 (MDR). In Finland, carfentanil has not been classified as a narcotic as of July 2017.

According to the EMCDDA-Europol Joint report (2017): "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)."

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other information pertinent to scheduling of the substance

None.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of Carfentanil

Please refer to separate Annex 1 document published on ECDD website