

Brussels, 23 November 2017
(OR. en)

14728/17

CORDROGUE 153
SAN 435
ENFOPOL 561

NOTE

From:	EMCDDA
To:	Delegations
No. prev. doc.:	11635/17
Subject:	Risk assessment report on a new psychoactive substance: Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4- carboxylate (carfentanil)

Following the Council's request to conduct a Risk Assessment on a new psychoactive substance: Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil), the EMCDDA hereby presents the above-mentioned Risk Assessment Report drawn up by its Scientific Committee pursuant to Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances.

**Risk assessment report on a new psychoactive substance:
Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil)**

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

Contents

1. Introduction 4

2. Physical, chemical and pharmacological description..... 6

3. Chemical precursors that are used for the manufacture 10

4. Health risks 10

5. Social risks 17

6. Information on manufacturing, trafficking, distribution, and the level of involvement of organised crime 19

7. Information on any assessment in the United Nations system..... 20

8. Description of the control measures that are applicable in the Member States 20

9. Options for control and the possible consequences of the control measures 22

10. Conclusion 23

11. List of annexes 25

1. Introduction

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (commonly known as carfentanil). The report is intended for policy makers and decision makers in the institutions of the European Union.

The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines ⁽¹⁾. It is written as a stand-alone document, which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on carfentanil, is provided below.

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

⁽¹⁾ EMCDDA (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, Publications Office of the European Union, Luxembourg. Available at: <http://www.emcdda.europa.eu/html.cfm/index100978EN.html>

⁽²⁾ OJ L 127, 20.5.2005, p. 32.

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

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

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

Carfentanil was formally notified on 12 February 2013 by the EMCDDA on behalf of the Latvian National Focal Point, in accordance with Article 4 of the Council Decision. The notification related to the seizure of 70.139 grams of light yellow powder seized on 8 December 2012 by police. Following an assessment of the available information on carfentanil, and, in accordance with Article 5 of the Council Decision, on 27 July 2017 the EMCDDA and Europol submitted a *Joint Report* on carfentanil ⁽⁶⁾ to the Council of the European Union, the European Commission, and the European Medicines Agency (EMA). Taking into account the conclusion of the *Joint Report*, and, in accordance with Article 6 of the Council Decision, on 14 September 2017 the Council formally requested that ‘the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification’.

In accordance with Article 6.2, the meeting to assess the risks of carfentanil was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of four additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of carfentanil, including health and social risks. A further four experts participated in the risk assessment: two experts from the Commission, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 08 November 2017 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol, and the EMA. A list of the extended Scientific Committee, as well as the list of other participants attending the risk assessment meeting, is annexed to this report (Annex 2).

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

- Technical report on Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil) (Annex 1);
- EMCDDA–Europol Joint Report on a new psychoactive substance: methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil) ⁽⁶⁾;
- Open source information including scientific articles, official reports, grey literature, internet drug discussion forums and related websites (hereafter ‘user websites’);
- Additional information provided during the course of the risk assessment meeting by the participants;
- The EMCDDA operating guidelines for the risk assessment of new psychoactive substances ⁽¹⁾; and,
- Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ⁽²⁾.

⁽⁶⁾ EMCDDA (2017), EMCDDA–Europol Joint Report on a new psychoactive substance methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil), EMCDDA, Lisbon.

Finally, it is important to note that this risk assessment report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with carfentanil. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify, and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. The EMCDDA's toxicovigilance system, which is a central component of the EU Early Warning System, has also been strengthened resulting in more information being available regarding serious adverse events associated with new psychoactive substances. Nonetheless, it is likely that these events remain under-detected and under-reported.

2. Physical, chemical and pharmacological description

Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil) is a 4-carboxylic acid methyl ester derivative of fentanyl. Carfentanil contains one basic nitrogen atom in the piperidine ring readily forming salts with organic or inorganic acids. Fentanyl analogues (fentanils) have in common an aralkyl group attached to a 4-*N*-acylanilinopiperidine.

Carfentanil is known from the scientific literature.

Pharmacologically, carfentanil is an opioid receptor agonist.

Synthetic opioids like fentanyl and related 4-anilinopiperidine derivatives are potent analgesics. Initially developed in the 1960's as part of research efforts to develop safer and better opioid analgesics, a small number of this family of compounds—alfentanil, fentanyl, sufentanil and remifentanyl—have become widely used in human medicine as adjuncts to general anaesthesia during surgery and for pain management. They are available in a wide variety of formulations, such as liquids for injection, tablets, transdermal patches, lozenges, and nasal sprays. Some are also used in veterinary medicine as general anaesthetics, for pain management, and, in the case of carfentanil and thiafentanyl, to immobilise large animals.

Fentanyl analogues first emerged on the illicit drug market in the United States of America in 1979. At the time they were not controlled under drug legislation. They were manufactured in clandestine laboratories and sold on the heroin market as heroin or 'synthetic heroin'.

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

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

Carfentanil as free base may occur as solids. No data on the physical properties of the hydrochloride salt are available. A carfentanil formulation for veterinary use was commercially available as its citrate salt under the trade name Wildnil®. Available data states that carfentanil is soluble in chloroform, dichloromethane, ethyl acetate, and, to some extent, in methanol. The high LogP (octanol-water distribution) indicates that carfentanil is a lipophilic compound.

In Europe, carfentanil has been seized as powder (ranging from white and pale yellow to brown); to a lesser extent it has also been seized as a liquid. In some cases it has been identified along with other substances, including other opioids. For example, carfentanil was detected in mixtures with heroin in over 30% of law enforcement seizures; in a small number of cases cocaine was present in addition to heroin and carfentanil.

The analytical identification of carfentanil in physical and biological samples is possible using several analytical techniques. These include chromatographic and mass-spectrometric techniques, and specific immunoassays.

Analytical reference materials are important for the correct identification and for facilitating the quantification of carfentanil in physical and biological samples. Such reference materials are commercially available. It should be noted that concentrations in blood samples can be in the sub-nanogram per millilitre range.

Carfentanil may not be part of most routine drug screenings and therefore may be under-detected and under-reported.

Route of administration and dosage

In Europe, carfentanil is currently typically administered by intravenous injection. This is because it is sold as or mixed with heroin or other opioids without users being aware. Carfentanil can also be administered orally as a powder, as tablets, or as a solution; it can also be administered intranasally or sublingually via spray or snorted (insufflated); inhaled by vaporising e-liquid type solutions ('vaping'); inhaled by smoking or vaporising the 'free base'; and administered transdermally. In view of its high potency, users may prepare diluted solutions for intranasal application using nasal sprays.

Limited information is available regarding the dose and the dose regimens of carfentanil. It is not possible to currently discern the 'typical' dosages administered by users. In addition, doses appear to differ depending on factors such as the route of administration, the tolerance of the users, the use of other drugs, and the desired effects.

Pharmacology

Studies investigating the binding and functional activity at opioid receptors *in vitro* for carfentanil show that it is a highly selective μ -opioid receptor agonist. Carfentanil has been extensively tested in animals, showing extremely high analgesic potency. Carfentanil is used to immobilise wildlife and zoo animals usually in combination with a α_2 -adrenoreceptor agonist.

When the agonist activity of the carfentanil is compared with that of morphine, its potency is much higher in tests *in vivo* (e.g., analgesia), than in tests *in vitro* (e.g., binding affinity for μ receptors). For example the analgesic potency of carfentanil has been reported to be up to 10,000 times that of morphine, while its affinity for μ receptors is only 14 to 135 times higher.

The pharmacokinetic properties of carfentanil are consistent with its high lipophilicity that results in rapid absorption and tissue distribution, including diffusion across the blood-brain barrier.

According to animal data and limited human data, carfentanil is readily absorbed following injection, transmucosal administration, or inhalation. It is widely distributed throughout the body and crosses the blood brain barrier. In regions of the brain with higher binding potential, carfentanil disappears gradually with the majority still remaining after 90 minutes. Systemically available carfentanil is rapidly metabolised showing similarities to fentanyl metabolism. Consequently drug-drug interactions observed with fentanyl might equally apply. Both, carfentanil and its metabolites, are excreted in urine.

The concomitant use of other central nervous system (CNS) depressants, including other opioids, sedatives/hypnotics, ethanol, pregabalin, gabapentin, tranquillisers, and sedating anti-histamines, may produce additive depressant effects.

Psychological and behavioural effects

From the available data, the psychological and behavioural effects of carfentanil share similarities with fentanyl and other opioid analgesics. Dizziness, drowsiness, and incoordination have been reported. Other effects common to opioids, such as relaxation and euphoria, can be expected; at higher doses, sedation and profound intoxication occur.

Legitimate uses

There is no marketing authorisation (existing, on-going, or suspended) for carfentanil in the European Union or in the Member States that responded to the request for information, which was undertaken as part of the Joint Report process. However, the data collection is incomplete and some countries indicated that this information is not known.

It is possible that the substance may have limited use in veterinary medicine in Europe based on a medicinal product that is prepared extemporaneously in accordance with national legislation.

Carfentanil is used in veterinary medicine as a tranquilising agent in zoological parks and wildlife environments to rapidly incapacitate large animals in order to facilitate veterinary procedures. Carfentanil was first introduced to the market for veterinary use in 1986. Carfentanil was marketed in the United States under the proprietary name Wildnil® and is approved by the United States Food and Drug Administration for use as an immobilising agent in certain animal species. Commercial production of Wildnil® ceased in 2003, and it appears that the substance is available only as a compounded dosage form.

There is no information to suggest that carfentanil is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not carfentanil is currently used in the manufacture of a medicinal product.

[¹¹C]Carfentanil is widely used as a selective radiotracer in animal and human positron emission tomography (PET) imaging studies of the μ -opioid system.

Carfentanil is also used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research.

There is currently no information that suggests carfentanil is used for any other legitimate purposes.

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

3. Chemical precursors that are used for the manufacture

Information on the chemical precursors and the synthetic methods employed for carfentanil detected on the drug market within the European Union is limited.

Carfentanil was first synthesised by a group of chemists at Janssen Pharmaceutica in 1974, using a method which was subsequently patented. A number of additional methods have been reported in the literature. The manufacture of carfentanil most likely relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl. Accordingly, methods developed for the synthesis of fentanyl are applicable to carfentanil. Most of these are straightforward, make use of common laboratory equipment and precursors, and require only basic knowledge of chemistry. The substance *N*-phenethyl-4-piperidone (NPP) and methyl 4-[phenyl(propanoyl)amino]piperidine-4-carboxylate could be used for the manufacture of carfentanil.

A pre-precursor of carfentanil and other fentanils, NPP, has been recently scheduled ⁽⁷⁾.

Due to the high potency of carfentanil there is a serious risk of severe poisoning following accidental exposure during its manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substance.

4. Health risks

Individual health risks

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

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

Carfentanil may be used in combination with other drugs (intentionally or unintentionally).

Information from law enforcement seizures and deaths reported to the EMCDDA show that carfentanil is being mixed with heroin, fentanyl, and other fentanils, sold on the illicit opioid market, and injected by opioid users (including heroin injectors). Many of the users will be unaware that they are using carfentanil. Drug injection is associated with health risks which include transmission of blood borne diseases.

⁽⁷⁾ Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.

While specific information for carfentanil is limited, of note is the apparent popularity of selling ready-to-use or using homemade nasal sprays containing solutions for the administration of fentanils. These typically contain milligram amounts of dissolved substance. The preparation of such solutions is inherently prone to mistakes in weighing and dilution which may lead to solutions with higher (or lower) concentrations. This may constitute an increased risk of acute toxicity to the individuals, who are unlikely to be able to control the dose being consumed.

In addition, recent seizures in Europe of nasal sprays containing other fentanils found that these have been sold in some cases as unlabelled bottles. In other cases, users have also filled nasal sprays previously containing medicines (such as nasal decongestants) with fentanils. The lack of labelling increases the potential for accidental use by others and therefore poses a risk of poisoning.

Acute toxicity

Safety pharmacological parameters have been studied both in laboratory animals and immobilised non-laboratory animals. Briefly, a common effect observed in many species is respiratory depression which may lead to respiratory arrest. The sensitivity to these effects differs greatly between species and those belonging to great apes are at greater risk of respiratory depression.

The most serious acute risk in humans arising from the use of carfentanil is rapid and severe respiratory depression, which can lead to apnoea, respiratory arrest, and death. Although the pharmacology and toxicology of carfentanil largely remains unstudied in humans, the available data suggests that the nature of its effects share similarities with opioid analgesics such as fentanyl. The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, and respiratory depression.

While there is limited data on the clinical features of poisoning caused by carfentanil, reported features include reduced level of consciousness or unconsciousness, respiratory depression and arrest, and miosis.

The timely administration of antidote naloxone will reverse acute poisoning caused by carfentanil. Recent clinical and community experience in treating poisonings caused by carfentanil suggests that larger than normal doses and repeated doses of naloxone may be required to manage the poisoning in some cases; longer periods of observation may also be required.

In general for fentanils, the risk of life-threatening poisoning may be exacerbated by: the difficulty in diluting/using fentanils (as they are typically highly potent), which can lead to a toxic dose being accidentally used; the apparent rapid onset of severe poisoning following use; using routes of administration that allow large amounts of the substance to rapidly reach the central nervous system (such as injecting, insufflation, and inhalation); availability of easy to use dosage forms (such as nasal sprays and e-liquids); lack of awareness and experience of users with these new substances (effects and dosage); use of other central nervous system depressants (such as other opioids, benzodiazepines, and alcohol); lack of tolerance to opioids in opioid-naïve persons (such as new or former users); use in environments where it may be difficult to summon help in the event of poisoning (e.g. alone in a home environment); and, limited availability of the antidote naloxone in community settings.

In addition, and, often unknown to users, the fentanils are sold as heroin or mixed with heroin. They are also used to make counterfeits of highly sought-after analgesics and benzodiazepines. They have also been sold in or as drugs such as cocaine. Due to this, users may not be aware that they are using a fentanyl; in some cases these individuals will have no tolerance to opioids nor access to community naloxone programmes. Overall, these factors may increase the risk of life-threatening poisoning.

Acute intoxications

In total, 3 acute intoxications with confirmed exposure to carfentanil were reported to the EMCDDA by France (2 cases) and Lithuania (1). The cases occurred in November 2016, January 2017, and May 2017.

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 hospitalisation of the patients. Naloxone was administered to the 3 patients; in at least 2 cases more than one dose was administered 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 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, the patient believed that they were taking carfentanil.

Information from other sources

Twenty nine cases of non-fatal intoxications with confirmed exposure to carfentanil were reported in the literature, mostly from the United States. Carfentanil blood concentrations were similar to those in fatal cases, on average below 1 ng/ml.

Deaths

A total of 61 deaths were reported by Belgium (1), Germany (1), Estonia (6), Finland (2), Lithuania (16), Norway (1), Sweden (3), and the United Kingdom (31 cases). Carfentanil was analytically confirmed from post-mortem samples in 55 deaths and carfentanil exposure was confirmed in all deaths.

Of the 38 deaths where demographic data were available, 32 were male (84%) and 6 were female (16%). The mean age of the males was 37 years (median 38) and ranged from 15 to 54 years. Where age was known, the females were aged 21, 28, 32, 45 years.

Where known, the deaths occurred between November 2016 and June 2017; the deaths in the United Kingdom deaths occurred between February 2017 and June 2017.

Cause of death and toxicological significance

The cause of death was reported in 6 cases, and, in 5 of these, intoxications with carfentanil was reported either as the cause of death or as likely to have contributed to death (even in presence of other substances). Where additional toxicology information was available, other substances were detected in practically all cases.

Carfentanil was quantified in 33 cases. Post-mortem blood concentrations ranged from 0.02 to 4.4 ng/mL blood (median 0.50 ng/mL blood). Due to the toxicity of potent opioids and variability in user tolerance, determination of a 'fatal' concentration based on a post-mortem blood concentration is not reliable. In the majority of circumstances involving fentanils, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use.

A range of other substances were detected in the deaths, including: cannabinoids, benzodiazepines, amphetamines, cocaine, antidepressants, antipsychotics, antihistamines, and ethanol, etc. In particular, markers of heroin use (i.e. morphine, codeine, noscapine, papaverine, 6-monoacetylmorphine) as well as other opioids (including tramadol, methadone, oxycodone and dihydrocodeine) were detected in the vast majority of deaths. In terms of fentanils; fentanyl, butyrylfentanyl, 4-fluorobutyrylfentanyl, furanylfentanyl, and alfentanil were detected in 23 deaths where additional toxicological information was available.

Overall, while other substances may have contributed some toxicity, a synergistic effect with carfentanil would have been likely with other central nervous system depressants such as ethanol, benzodiazepines, opioids (including other fentanils), etc. Nevertheless, the highly potent opioid nature of carfentanil means that the primary toxic contribution could be attributed to carfentanil and death may not have occurred if carfentanil had not been used (even where heroin was used that may not have exceeded the deceased's toxicity threshold). An assessment of the toxicological significance score (TSS) ⁽⁸⁾ incorporating the above considerations, shows that carfentanil had a TSS value of 3 (high) in 35 out of 36 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining death, fentanyl was potentially the primary substance and carfentanil was deemed to be a secondary finding (TSS value of 2, medium). There was insufficient information available for the other cases to allow appropriate TSS assessment.

⁽⁸⁾ Elliott, S., Sedefov, R. and Evans-Brown, M. (2017), 'Assessing the toxicological significance of new psychoactive substances in fatalities', Drug Testing and Analysis. <https://doi.org/10.1002/dta.2225>

Circumstances of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication). Drug paraphernalia (e.g. syringes) were reported as being present (often *in situ* and close by) in many cases, with some decedents still holding the equipment or a needle in the arm—suggesting that death may have occurred suddenly after administration. Whilst this is not uncommon with heroin deaths in general, it is a sign of the tolerance and toxicity threshold being reached and exceeded, likely due to the increased potency of the fentanils contributing to the opiate/opioid toxic burden.

Information from other sources

More than 800 deaths with confirmed exposure to carfentanil have been reported in the United States in the past few years. In some of these cases, carfentanil was reported as the cause of death or contributing to the death.

Ability to operate machinery and drive

There have been no studies of the effects of carfentanil on the ability to drive and operate machines. However, it is well established that opioid narcotic analgesics, such as fentanyl, impair the mental and physical ability required to drive and operate machines. This effect extends to carfentanil; with carfentanil positive cases of suspected driving under the influence of drugs have been reported in the literature.

Chronic toxicity

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

Abuse liability and dependence potential

No studies have investigated the abuse liability or dependence potential of carfentanil in humans.

Available data show that carfentanil is a potent opioid able to suppress withdrawal symptoms in morphine-dependent rhesus monkeys, but not in rats. In limited studies in rats and rhesus monkeys physical dependence and self-administration were not observed and carfentanil did not generalise with a κ or μ opioid receptor agonist in drug discrimination test.

However, given what is currently known about carfentanil pharmacology, including some similarities to other fentanils and opioid narcotic analgesics, it may have a potential for abuse and dependence. Further research will be required in order to determine such effects.

Public health risks

The public health risks associated with carfentanil may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences. Detailed information, including data on sporadic versus chronic use, that allow for a determination of public health risks associated with carfentanil are not available. In addition, risk of accidental exposure needs to be considered.

Extent, frequency, and patterns of use

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

In at least three Member States, carfentanil is being sold on the illicit opioid market, typically in mixtures with heroin, fentanyl, and/or other fentanils. In these cases, it is reasonable to assume that these individuals will not be aware that they are using carfentanil.

Based on its known pharmacology and that it is sold as a 'legal' replacement to illicit opioids, it would be expected that carfentanil may be sought by those looking for substitutes to opioids, such as heroin and prescription opioids. It also appears that there is interest in this substance by some psychonauts.

Availability and quality on the market

While carfentanil was first detected in Europe in December 2012, in the past two years there has been an increase in the availability of the substance as well as seizures by law enforcement. In total, more than 800 seizures have been reported by seven Member States; approximately 25% of the seizures were made in the first half of 2017. Most of the seizures have been made by police at street-level, with some seizures being made in custodial settings. Typically, carfentanil was seized as a powder; in some cases it has also been seized as a liquid. In over 25% of seizures, carfentanil was the only substance reported as detected; while in more than 30% of the seizures, carfentanil was detected in mixtures with heroin. The largest single seizure of carfentanil was 440 grams of 'unadulterated' carfentanil in powder form made by police in the United Kingdom in May 2017.

It is important to note that as carfentanil is not routinely screened for it will be under-detected and under-reported.

The available data suggests that carfentanil is sold on the surface web and darknet in small and bulk quantities. Typically it is offered as a powder and may be advertised as a 'research chemical' or/and as a 'pharmaceutical intermediate'.

Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviours of users of carfentanil. While no specific examples are available on the possible appeal of the substance, the available information from law enforcement seizures and deaths reported to the EMCDDA shows that in some countries carfentanil is being mixed with heroin and/or other opioids and used by those who inject heroin/opioids. Many of these users will be unaware that they are using carfentanil.

More generally, it is reasonable to assume that carfentanil may be sought by those looking for 'legal' substitutes for illicit opioids, such as heroin and/or prescription opioids. There also appears to be some interest in the substance from psychonauts.

Nature and extent of health consequences

The available information shows that established opioid injectors (including heroin injectors) are using carfentanil. Drug injection is associated with health risks which include transmission of blood borne diseases.

In addition to the individual health risks that are discussed above, there are some further considerations related to the fentanils as a group that should be considered in respect to potential risks to public health.

Mirroring the increased availability of fentanils on the drug market over the past few years, there has also been an increase in the number of outbreaks of mass poisoning caused by fentanils, particularly in the United States and Canada. These types of outbreaks have had the potential to overwhelm emergency responders and other local healthcare systems, as well as deplete stocks of naloxone. Stocks and availability of the naloxone, as well as adequacy of training in how to resuscitate poisoned patients both in clinical and community settings may need to be assessed. This might also include a review of the availability of naloxone to users through take-home naloxone programmes.

As noted, the open sale of fentanils on the surface web and darknet marketplaces along with the use of new dosage forms—such as ready-to-use nasal sprays and e-liquids for vaping—add to the complexity of the problem caused by this group of substances. They have become easier to get hold of and easier to use. The Committee is concerned about whether the availability of 'novel' dosage forms has the potential to make the use of fentanils more socially acceptable.

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

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

Accidental exposure to fentanils may also pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those in custodial settings and postal services. Where necessary, specific risks should be identified and assessed, and, appropriate measures to reduce these risks should be implemented. This may include appropriate protective equipment, training in resuscitation, and making naloxone readily available to relevant personnel in sufficient quantities in the event of poisonings. Any required measures should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose.

Long-term consequences of use

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

Conditions under which the substance is obtained and used

There is limited information on the conditions which carfentanil is obtained and used. Carfentanil has been sold on the surface web and darknet marketplaces, typically as powders in small and bulk quantities. In addition, carfentanil has also been mixed with heroin, fentanyl, and other opioids and then sold on the illicit opioid market. In most cases users will be unaware that they are using carfentanil. This presents an inherent risk to the individuals.

In addition, information suggests that carfentanil may be deliberately sought by some users. These include psychonauts and others who are experimenting with the substance (for example for its analgesic effects).

5. Social risks

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

When considering the possible social risks of the substance it is important to consider that the evidence from law enforcement seizures and death cases show that it is being used by people who inject opioids, including heroin. It is likely that many of these users are unaware that they are using carfentanil.

Individual social risks

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

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

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

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

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

As discussed above, accidental exposure of fentanils, and in particular carfentanil, may pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those in custodial settings and postal services.

Economic costs

There are no data on the effects of carfentanil in respect to its health and social costs.

Possible appeal to specific population groups

Whilst no specific examples are available on the possible appeal of carfentanil to user groups, the substance is being used by people who inject opioids, including heroin. It is likely that many of these users are unaware that they are using carfentanil.

In addition, it is reasonable to assume that the substance may be sought by those looking for substitutes for illicit opioids, such as heroin and/or prescription opioids.

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

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

There is limited information on the involvement of organised crime or established criminal groups in the manufacture, distribution, and supply of carfentanil. In this respect, Estonia reported that almost all trafficking and distribution of fentanils, including carfentanil, is linked with organised crime groups in the country. In addition, they reported that these groups are keeping dealers under control through violence.

The United Kingdom reported to Europol 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. The United Kingdom also reported that they had 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 milligrams (15 orders) to 1 gram (1 order).

In the cases reported to Europol where the country of origin for the seizures was known, the countries were China (specifically Hong Kong), and, to a lesser extent, the United Kingdom and Germany.

Germany reported a seizure of carfentanil by Canadian law enforcement in Vancouver, in June 2017. The carfentanil was detected in a package which was *en route* from Hong Kong to Canada via Germany, using express mail/courier service.

Lithuania reported that there are indications that carfentanil may be imported from Russia or China. They also reported that carfentanil is often mixed with heroin and prepared for heroin users and most cases are related to heroin distribution in the local Roma community.

Sweden indicated that carfentanil has been bought from internet vendors and delivered directly to the user from China, the United Kingdom and Germany. They reported that there are no indications of the domestic sale of carfentanil in Sweden.

The United Kingdom reported that it was unclear how much, if any, carfentanil has been manufactured domestically. Information indicates that it has been shipped from China/Hong Kong and the substance has been used as received, or mixed with other drugs, for example heroin, or cutting agents before being used or sold on.

Latvia reported 6 seizures of carfentanil to the EMCDDA which occurred inside a prison or custodial setting.

The seizure of an illicit laboratory in Europe in 2013 that was producing fentanils demonstrates the capability to manufacture fentanils exists within the European Union.

7. Information on any assessment in the United Nations system

The World Health Organization (WHO) is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971. In May 2017, the WHO informed the EMCDDA that carfentanil will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017.

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

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

- In Belgium, carfentanil is controlled by Royal Decrees of 31 December 1930 and 22 January 1998.
- In Cyprus, carfentanil is controlled as a Class A drug within the Narcotic Drugs and Psychotropic Substances Law 1977.
- In the Czech Republic, carfentanil is controlled since April 2011.
- In Denmark, carfentanil is controlled since 24 November 2016 by an amendment of the Executive Order on Euphoriant Substances.
- In Estonia carfentanil is controlled by way of generic definition.
- In France, carfentanil is controlled as of 5 September 2017.
- In Germany, carfentanil is controlled under schedule I (narcotics not eligible for trade and medical prescription) of the German Narcotics Act (Betäubungsmittelgesetz, BtMG).
- In Ireland, carfentanil is listed in schedule 2 of the Misuse of Drugs Act.
- In Latvia, carfentanil is included in the Cabinet Regulation N 847 'Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be Controlled in Latvia' and the law 'On the Procedures for the Coming into force and Application of the Criminal Law'.

- In Lithuania, carfentanil is subjected to control measures by The Republic of Lithuania Minister of Health Order No V-267 (21/02/2014) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000'.
- In Sweden, carfentanil is regulated as a narcotic since 1982.
- In the United Kingdom, carfentanil is controlled under the Misuse of Drugs Act 1971 as well as by way of a generic definition.
- In Turkey, carfentanil is controlled as of 23 May 2014.
- In Norway, carfentanil is listed as a 'prohibited substance'.

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

- In Austria, carfentanil is covered by the phenethylamine generic definition within the Austrian Act on New Psychoactive substances.
- In Hungary, carfentanil is controlled by way of generic definition within the Ministry of Human Resources decree 55/2014.
- In Poland, carfentanil is controlled according to the general definition of the 'substitute drug' (Act of 8 October 2010 amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection, Journal of Laws "Dz.U." No. 213, item 1396). Pursuant to Article 44b of the Act on counteracting drug addiction, it is prohibited to manufacture and introduce substitute drugs to trade.

Finland reported that carfentanil is controlled under medicines legislation.

Twelve Member States (Bulgaria, Croatia, 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.

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

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

Carfentanil was controlled in China as of the 1 March 2017. This control measure may at least deter the open manufacture and sale of this substance by chemical companies in this country, which are linked to the supply of the substance in Europe.

There are no studies on the possible consequences of such control measures on carfentanil. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- Considering the use of carfentanil in PET studies, this control option could affect the use of this compound in scientific research.
- Considering the possible limited use of extemporaneously produced carfentanil, this control option could affect veterinary practice.
- This control option could be expected to limit the availability of carfentanil and hence the further expansion of the current open trade in this substance.
- A health consequence that might result from this control option is the benefit brought about by the presumed reduction in availability and use.
- This control option could facilitate the detection, seizure and monitoring of carfentanil related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies across the European Union.
- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement, and the courts.
- This control option could lead to replacement with other (established or new) psychoactive substances, which may in themselves have public health consequences and social risks.
- This control option could create an illicit market in carfentanil with the increased risk of associated criminal activity, including the involvement of organised crime.

- This control option could impact on both the quality/purity and price of any carfentanil still available on the illicit market. The extent to which this will impact on public health, criminality, or levels of use, is difficult to predict.
- It is difficult to predict the impact of this control option on current or future research by the pharmaceutical or chemical industries.
- In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of carfentanil on the market post-control, should this control option be pursued.
- Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include restricting the importation and supply of the substance as some Member States have already done.

10. Conclusion

Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil) is a synthetic opioid and is structurally related to fentanyl, a controlled substance widely used in medicine as an adjunct to general anaesthesia during surgery and for pain management. Carfentanil is one of the most potent narcotic opioid analgesics.

In Europe, the substance is currently typically administered by intravenous injection. Other routes of administration, including use of nasal sprays, orally and nasal insufflation have also been reported. Carfentanil was mixed with heroin in more than 30% of the seizures reported by law enforcement.

Sixty-one deaths with confirmed exposure to carfentanil have been reported by 8 Member States. Many of the deaths involved high-risk drug users, including heroin injectors. Other drugs, including morphine and other fentanils, were also detected in many of the cases. In at least 6 of the deaths carfentanil was reported to be either the cause of death or to have contributed to death; in many of the remaining cases the investigation into the death is ongoing. There have also been reports of more than 800 deaths from the United States; in at least some of these cases carfentanil was the cause of death or contributed to death.

Similar to other opioid analgesics, the most serious acute risk arising from the use of carfentanil is rapid and severe respiratory depression, which can lead to apnoea, respiratory arrest, and death.

Naloxone is an effective antidote to poisoning caused by carfentanil. Treatment may require repeated doses of naloxone.

It is important to note that detections of carfentanil may be under reported since the substance is not routinely screened for. Routine commercially available immunoassays may not detect this compound.

Information from law enforcement seizures as well as investigations into deaths shows that carfentanil is being used by opioid injectors, including those that use heroin.

Accidental exposure to carfentanil, as well as to other fentanils, may pose a risk to law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as to those in custodial settings and postal services. Where necessary, specific risks and appropriate measures to reduce these risks should be identified and implemented. Any required measures should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose.

There is limited information on the involvement of organised crime or established criminal groups in the manufacture, distribution and supply of carfentanil. In this respect, Estonia reported that almost all trafficking and distribution of fentanils, including carfentanil, are linked with organised crime groups in Estonia. In addition, they reported that these groups are keeping dealers under control through violence.

There is limited information on the chemical precursors and the synthetic routes used to manufacture the carfentanil detected within the European Union. Most of the synthetic routes are straightforward, make use of common laboratory equipment and readily available precursors, and require only basic knowledge of chemistry. Information from seizures suggests that some carfentanil on the market in Europe has been produced by chemical companies based in China.

There is no marketing authorisation (existing, on-going, or suspended) for carfentanil in the European Union or in the Member States that responded to the request for information, which was undertaken as part of the Joint Report process. However, the data collection is incomplete and some countries indicated that this information is not known.

Carfentanil is authorised as a veterinary medicine in the United States for the immobilisation of large animals. It is possible that the substance may have limited use in veterinary medicine in Europe based on a medicinal product that is prepared extemporaneously in accordance with national legislation.

A radiolabelled form of carfentanil is widely used in scientific research. Carfentanil is also used as an analytical reference standard and in scientific research.

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

Twelve Member States, Turkey, and Norway control carfentanil under drug control legislation. Four Member States control carfentanil under other legislation.

As for any new psychoactive substance, many of the questions related to carfentanil that are posed by the lack of data on the risks to individual health, risks to public health, and social risks, could be answered through further research. Areas where additional information would be important include studies on: rationale for use, prevalence and patterns of use (including studies that examine user groups and risk behaviours); the market; chemical profiling; complete pharmacological profiling; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between carfentanil and other substances; the dependence and abuse potential; and the public health risks associated with its use.

The Committee notes that a decision to control carfentanil has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks and consequences arising from the use of carfentanil. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, since carfentanil was first detected at least twenty new fentanils and a number of other new opioids that may replace it are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation.

Finally the Committee notes that it is important to continue to collect and disseminate accurate information on carfentanil to users, practitioners, policy makers, decision makers and those who may be at risk of accidental exposure. An additional challenge in respect to reducing risk in users and potential users is the balance between providing information to prevent harm and the unintended consequences of communicating the risks of opioids. There is evidence that using terms to describe them as 'potent', 'strong', 'deadly', and 'toxic' can lead some individuals to specifically seek out these substances. Such unintended promotion of the substances may also extend to former users and other groups.

11. List of annexes

Annex 1: Technical report on Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil).

Annex 2: List of participants at the risk assessment meeting of Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil).

DRAFT**Technical report on methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil)**

Parts of this technical report were prepared under contract from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Given the time frame stipulated in the Council Decision, additional data presented and discussed during the preparatory meeting for the risk assessment and the risk assessment meeting have not yet been incorporated into the technical report. In addition, this technical report has not been formally edited by the EMCDDA. As such, this report should be regarded as a draft document until such time that the final version is produced by the EMCDDA which will incorporate the additional data and which will be formally edited. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The *Risk assessment report on a new psychoactive substance: methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil)* to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

3 November 2017

Annex 1 to the *Risk Assessment Report on methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil)*

Table of contents

Introduction	28
Section A. Physical, chemical, pharmaceutical and pharmacological information	30
A1. Physical, chemical, and pharmaceutical information	30
A2. Pharmacology, including pharmacodynamics and pharmacokinetics	41
A3. Psychological and behavioural effects	65
A4. Legitimate uses of the product	66
Section B. Dependence and abuse potential.....	67
B1. Animal data	67
B2. Human data.....	68
Section C. Prevalence of use	68
Section D. Health risks.....	74
D1. Acute health effects	74
D2. Chronic health effects	108
D3. Factors affecting public health risks.....	109
Section E. Social Risks	112
E1. Individual social risks	112
E2. Possible effects on direct social environment.....	112
E3. Possible effects on society as a whole.....	112
E4. Economic costs	112
E5. Possible effects related to the cultural context, for example marginalisation	112
E6. Possible appeal of the new psychoactive substance to specific population groups within the general population	112
Section F. Involvement of organised crime	113
F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain.....	113
F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances.....	114
F3. Evidence of the same groups of people being involved in different types of crime	114
F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety).....	114
F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society.....	114
F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)	115
F7. Use of violence between or within criminal groups	115
F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation	115
References	115

Introduction

In accordance with Article 5 of the Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances ⁽⁹⁾, on 18 May 2017, the EMCDDA and Europol launched the Joint Report procedure for methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil) on the basis of data reported by the Member States to the European Union Early Warning System in accordance with Article 4 of the Council Decision. The information collection process for the Joint Report was completed in June 2017. The report was submitted to the EU Institutions on 27 July 2017 (EMCDDA, 2017a). In accordance with Article 6 of the Council Decision, on 14 September 2017, the Council of the European Union requested that a risk assessment on carfentanil should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for the risk assessment, and, to facilitate the risk assessment process, the EMCDDA is responsible for the collection and analysis of data on the substance to be assessed as well as drafting a technical report. This technical report has been prepared for the risk assessment of carfentanil that will be held at the EMCDDA premises in Lisbon on Wednesday 8 November 2017.

Some of the sections in this report were prepared under EMCDDA contracts (ref. CT.17.SAT.0103.1.0 and CT.17.SAT.0110.1.0).

Data sources

The information in this technical report is derived from:

- data reported by the Member States, Turkey, and Norway to the EMCDDA and Europol in accordance with Council Decision 2005/387/JHA (EMCDDA, 2017a); and,
- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, online drug discussion forums and related websites, and online vendors selling carfentanil.

Search strategy

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

⁽⁹⁾ OJ L 127, 20.5.2005, p. 32.

Medline and Web of Science were searched for 'carfentanil', 'carfentanyl', and the IUPAC name of this compound stated in this document. Publications retrieved by exact structure-based search in SciFinder® ⁽¹⁰⁾ have also been included where appropriate. The references were screened for relevance and included in the review where appropriate. Additional references were gathered from the sources mentioned in the collected papers.

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.

Note

It is important to note that when interpreting the information on self-reported user experiences in this report, it is not possible to confirm the specific substance(s) that have been claimed to be used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. Moreover, the actual composition of the substance/product may differ over time and different geographical areas. In addition, the information provided on user websites may not necessarily be representative of other users of carfentanil and should be regarded as illustrative only. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with due caution.

Reported prepared by

Leon van Aerts ⁽¹¹⁾, Simon Elliott ⁽¹²⁾, Michael Evans-Brown ⁽¹³⁾, Helgi Valur Danielsson ⁽⁵⁾, Anabela Almeida ⁽⁵⁾, Rachel Christie ⁽⁵⁾, Rita Jorge ⁽⁵⁾, Sofia Sola ⁽⁵⁾, Ana Gallegos ⁽⁵⁾, and Roumen Sedefov ⁽⁵⁾.

Acknowledgements

The EMCDDA would like to extend their sincere thanks and appreciation to: the Early Warning System (EWS) correspondents of the Reitox national focal points and experts from their national early warning system networks; the Europol national units and Europol Project Synergy; and, Dr István Ujváry, iKem BT, Budapest, Hungary for reviewing some of the sections of this report.

⁽¹⁰⁾ American Chemical Society, Chemical Abstract Service.
⁽¹¹⁾ Medicines Evaluation Board, Utrecht, Netherlands.
⁽¹²⁾ Alere Forensics, Malvern, Worcestershire, United Kingdom.
⁽¹³⁾ European Monitoring Centre for Drugs and Drug Addiction.

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

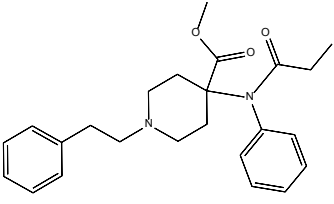
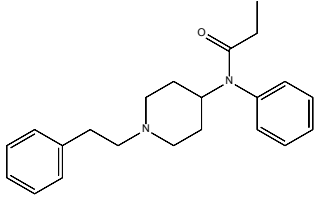
A1.1. Physical and chemical description

Chemical description and names

Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil) is a 4-carboxylic acid methyl ester derivative of *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propionamide (fentanyl). Carfentanil does not contain a chiral centre. The molecular structure, molecular formula, and molecular mass of carfentanil are provided in Figure 1.

Carfentanil belongs to the 4-anilidopiperidine class of synthetic opioids.

Fentanyl and a number of fentanyl analogues ⁽¹⁴⁾ are internationally controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol. Two additional fentanils ⁽¹⁵⁾ have recently subjected to risk assessment by the extended Scientific Committee of the EMCDDA (EMCDDA, 2017b; EMCDDA, 2017c).

i) Figure 1. Molecular structure, molecular formula, and molecular mass of carfentanil. The structure of fentanyl is provided for comparison.	
ii) Carfentanil	iii) Fentanyl
iv) 	v) 
vi) C ₂₄ H ₃₀ N ₂ O ₃	vii) C ₂₂ H ₂₈ N ₂ O
viii) 394.52 g/mol	ix) 336.48 g/mol

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

⁽¹⁵⁾ *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) and *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl).

Carfentanil, which is also known as 4-carbomethoxyfentanyl, has two positional isomers: 2- and 3-carbomethoxyfentanyl (¹⁶). These positional isomers differ in the position of the methoxy-carbonyl moiety on the piperidine ring. The synthesis and characterisation of 3-carbomethoxyfentanyl is reported in the literature (Mićović et al., 1998).

Names and other identifiers

Systematic International Union of Pure and Applied Chemistry (IUPAC) names:

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

Chemical synonyms:

4-((1-Oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid methyl ester

4-Piperidinecarboxylic acid, 4((1-oxopropyl)phenylamino)-1-(2-phenylethyl)-, methyl ester

Methyl 1-phenylethyl-4-(N-phenylpropionamido)isonipecotate

Methyl 4-(N-(1-oxopropyl)-N-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylate

Methyl 4-(N-propionyl-N-phenylamino)-1-(2-phenylethyl)-4-piperidine-carboxylate

Methyl 1-(2-phenylethyl)-4-[phenyl(propionyl)amino]piperidine-4-carboxylate

Other names:

4-Methoxycarbonylfentanyl

4-Carbomethoxyfentanyl

3-Demethyllofentanil

R33799 (citrate)

NIH 10570

(¹⁶) Throughout this report, 'carfentanil' refers to 4-carbomethoxyfentanyl.

R 31 833

R31833 (base)

DEA No. 9743

FDA Unique Ingredient Identifier: UNII:LA9DTA2L8F; 7LG286J8GV (citrate salt)

ChEBI ID: CHEBI:61084

CHEMBL compound ID: ChEMBL 290429

Commonly used names:

Carfentanyl

Carfentanil

Chemical Abstract Service Registry Numbers (CAS RNs) ⁽¹⁷⁾:

59708-52-0 (free base)

60645-15-0 (free base, alternative CAS RN)

61380-27-6 (citrate salt)

61086-44-0 (oxalate salt)

PubChem CID ⁽¹⁸⁾:

62156

⁽¹⁷⁾ 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.
⁽¹⁸⁾ <https://pubchem.ncbi.nlm.nih.gov/compound/62156>

IUPAC International Chemical Identifier Key (InCHI Key) ⁽¹⁹⁾:

YDSDEBIZUNNPOB-UHFFFAOYSA-N

SMILES ⁽²⁰⁾:

O=C(C1(CCN(CC1)CCC2=CC=CC=C2)N(C(CC)=O)C3=CC=CC=C3)OC

International Nonproprietary Name (INN):

Carfentanil (English INN)

Carfentanila (Spanish INN)

Carfentanilum (Latin INN)

карфентанил (Russian INN)

كارفانتانيل (Arabic INN)

卡芬太尼 (Chinese INN)

Proprietary names:

Wildnil®

Street names:

C.50 ⁽²¹⁾

Gray death ⁽²²⁾

⁽¹⁹⁾ InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

⁽²⁰⁾ The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

⁽²¹⁾ Norway reported a collected sample of carfentanil to the EMCDDA that was detected in powder from a zip-lock bag that was labelled 'C.50'.

⁽²²⁾ 'Gray Death', a street drug resembling concrete that surfaced late 2016 in Hamilton County, is often laced with heroin, fentanyl, carfentanil, furanyl fentanyl or acrylfentanyl (Coroner: Carfentanil resurfaces, 'Gray Death' and cocaine mixed with fentanyl hit the streets - WCPO Cincinnati, OH," n.d.).

Identification and analytical profile

Carfentanil has been seized in powder form and as a liquid (EMCDDA, 2017a) ⁽²³⁾. In some cases it has been identified along with other substances, including other opioids.

Approximately 2.7 kg of powders containing carfentanil have been seized in Europe. In at least 278 seizures, carfentanil was mixed with heroin. Carfentanil has also been detected in mixtures with other opioids: fentanyl (81 cases), methadone (13), fentanyl and furanylfentanyl (10), fentanyl and acrylylfentanyl (7), furanylfentanyl (4), tramadol (3) and acrylylfentanyl (2). In 4 cases, cocaine was present in addition to heroin and carfentanil (EMCDDA, 2017a).

In seizures, carfentanil was frequently found in ranging from white and pale yellow to brown.

In the United States, the Drug Enforcement Administration Special Testing and Research Laboratory has provided an overview of confirmed carfentanil cases examined by local, state, and federal forensic laboratories during 2016. Of 407 cases, 67 contained carfentanil only. Other substances contained were fentanyl (5 cases), furanylfentanyl (8), heroin (27), heroin/fentanyl (12), heroin/furanylfentanyl (1), heroin/fentanyl/furanylfentanyl (4), and other controlled substances (10) (including cocaine, U-47,700, methamphetamine, FUB-AMB and other cannabinoids). The remaining 273 cases did not contain detailed reporting (Casale, Mallette, & Guest, 2017).

Detailed laboratory analyses are necessary to identify the substance.

Physical description

Carfentanil (base) is described as a white powder (SWGDRUG, 2016) or pale yellow solid (Toronto Research Chemicals Inc., 2011). The reported melting points of carfentanil base are 92–93 °C (Janssen and Van Daele, 1979) and 94.9 °C (Walz et al., 2014). The reported logP values ⁽²⁴⁾ are 3.85 (Tollenaere et al., 1986) and 3.58 (Henriksen et al., 2005). The pKa value, measured at 20 °C, was found to be 8.10 (Tollenaere et al., 1986). No data for the boiling point or other physical characteristics were found in the literature. The high LogP:Octanol-water indicates that carfentanil is a lipophilic compound.

⁽²³⁾ A seizure of carfentanil in plant material has also been reported to the EMCDDA.

⁽²⁴⁾ LogP is logarithmic measure of the lipophilicity of a compound by its partition coefficient between an apolar solvent (here 1-octanol) and an aqueous buffer.

The Material Safety Data Sheet (MSDS) for carfentanil from Toronto Research Chemicals states that the melting/freezing point of carfentanil is 98–100 °C (Toronto Research Chemicals Inc., 2011). According to this MSDS, carfentanil is soluble in chloroform, dichloromethane and ethyl acetate. Cayman Chemical offers a 0.1% solution of carfentanil in methanol, indicating the substance is soluble in this solvent to this extent (Cayman Chemical, 2016). Similarly, Cerilliant offers a 0.1% methanol solution of the oxalate salt of carfentanil (Cerilliant, n.d.).

A carfentanil formulation for veterinary use was commercially available as its citrate salt (US FDA, n.d.) under the trade name Wildnil®. The melting point is 152.2 °C (Janssen & van Daele, 1979).

The melting point for carfentanil oxalate is reported as between 182 and 189.5 °C (Marton et al., 2012; Van Daele et al., 1976).

Analyses of seized powders in the United States suggest that illicit carfentanil entered the country as a hydrochloride salt (Casale, Mallette, & Guest, 2017). No data on the physical properties of this salt are available.

Chemical stability and typical reactions

The MSDS for carfentanil from Toronto Research Chemicals and Cayman Chemical indicate that no data on reactivity are available, but that the compound or the 0.1% solution in methanol, respectively, are stable under recommended storage conditions (Cayman Chemical, 2016; Toronto Research Chemicals Inc., 2011).

Extracted biological samples that were positive for carfentanil, stored in a refrigerated auto-sampler (8 °C) and re-injected on Ultra-High Performance Liquid Chromatography (UHPLC) after 24 and 48 hours showed no loss of signal, indicating good stability under these conditions (Shoff et al., 2017).

Analytical profile

Since carfentanil has been studied as an immobilisation agent in animals and used as a research tool for opioid research, many papers contain information on analytical methods. In Table 1, recently developed methods in forensic and analytical toxicology (mainly LC tandem MS) are summarised.

x) Table 1. Analytical methods for the detection of carfentanil.					
xi) Method	xii) LOD	xiii) LLOQ	xiv) Matrix	xv) Comments	xvi) Reference
xvii) UHPLC-Ion Trap-MS ⁿ	xviii) 0.1 ng/mL	xix) N.A.	xx) Blood, urine, liver, brain	xxi) Qualitative screening method	xxii) Shoff et al., 2017
xxiii) LC-MS-MS	xxiv) 0.05 ng/mL	xxv) 0.1 ng/mL	xxvi) Blood, vitreous humour	xxvii) Quantitative method	xxviii) Sofalvi et al., 2017
xxix) LC-MS-MS	xxx) 0.005 ng/mL	xxxi) 0.01 ng/mL	xxxii) Blood	xxxiii) Quantitative method	xxxiv) Shanks & Behonick, 2017
xxxv) LC-MS-MS	xxxvi) 0.01 ng/mL	xxxvii)	xxxviii) Blood, urine	xxxix) No detailed description of method	xl) Seither & Reidy, 2017
xli) HPLC-API-MS-MS	xlii) 0.003 ng/mL	xliii)	xliv) Urine	xliv) LOD norcarfentanil 0.027 ng/mL	xlvi) Wang & Bernert, 2006
xlvi) LC-MS-MS	xlvi) 0.03 ng/mL	xlix)	l) Blood	li) No detailed description of method	lii) Papsun et al., 2017
liii) NACE-ESI-MS ⁿ	liv) 0.55 ng/mL	lv)	lvi) Forensic exhibits	lvii)	lviii) Rittgen et al., 2012
lix) ELISA	lx) 0.5 ng/mL	lxi)	lxii) Serum	lxiii) fentanyl antibody-coated nanoparticles. Cross-reactivity with carfentanil 85%	lxiv) Mao et al., 2006
	lxv) 1 ng/mL	lxvi)	lxvii) Urine		

Carfentanil may go undetected in routine screening assays such as the *Immunoanalysis ELISA fentanyl assay* due to lack of cross-reactivity or because the concentration is below the limit of detection (Shoff et al., 2017; Sofalvi et al., 2017). It is therefore necessary to use specific and sensitive screening and quantification analytical techniques. Immunoassays kits developed specifically for carfentanil are available.

Nuclear magnetic resonance (NMR) spectroscopic characterisation of carfentanil has been published (Marton et al., 2012; Walz et al., 2014; SWGDRUG, 2016); infrared and mass spectroscopy spectra have also become available (SWGDRUG, 2016).

Methods and chemical precursors used for the manufacture

The methods of synthesis, precursors and main reagents used for the manufacture of carfentanil are summarised in Table 2.

Carfentanil was first synthesised by a group of chemists at Janssen Pharmaceutica on May 2, 1974 (Stanley, Egan, & Van Aken, 2008). An initial description of the route of synthesis for carfentanil used in the context of the preparation of a wide range of fentanyl derivatives for explorative purposes was published in 1976 (Van Daele et al., 1976). Subsequently Janssen Pharmaceutica patented a method in 1979. The latter synthesis consists of eight steps, among which is the preparation of a key α -aminonitrile via a Strecker reaction from 1-phenethyl-4-piperidone (NPP) ⁽²⁵⁾. This α -substituted nitrile must be hydrated and the obtained amide hydrolyzed, the aniline acylated and finally the acylamino acid must be methylated (Malaquin et al., 2010). This route of synthesis reportedly gives a low yield (Malaquin et al., 2010; Marton et al., 2012). An improved method for the conversion of the aminonitrile intermediate to the corresponding amino ester has been published (Taber & Rahimizadeh, 1992).

In a novel route, the α -aminonitrile is prepared by an anhydrous Strecker reaction and subsequently reacted with chlorosulfonyl isocyanate and methylene chloride, followed by cyclization of the resulting amide by treatment with 1 M HCl to yield a 1-phenyl-spirohydantoin derivate. Alkaline hydrolysis of the 2,4-imidazolidinedione derivative yielded α -amino acid in an overall yield of 39%. Finally the acylamino acid must be converted to its methyl ester (Feldman & Brackeen, 1990)

An alternative method for the synthesis of fentanyl, known as the Siegfried method, has been mentioned in the literature in which NPP is used as starting material (Lurie et al., 2012; Siegfried, n.d.). Such a method has been published also for the synthesis of carfentanil (Lu et al., 1990; Reiff and Sollman, 1992) and its analogues (Wen et al., 1993).

A simple two-step method known as the Ugi multicomponent reaction provides a 70% yield under optimal conditions (Malaquin et al., 2010).

Additional methods for the preparation of radiotracers have been described in the literature as well (Blecha et al., 2017; Dannals et al., 1985; Jewett, 2001; Saji et al., 1992; Shao et al., 2011; Shao et al., 2014; Shao & Kilbourn, 2009; Wang et al., 2011; Zhang et al., 2011). The desmethyl, that is the free acid derivative of carfentanil, 4-((1-oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid, is an important starting material for the synthesis of the radiotracers. Marton et al., 2012 reported various routes of synthesis to prepare this precursor.

N-Phenethyl-4-piperidone (NPP) was scheduled in 2017 and is listed in Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988. The scheduling came into force on 18 October 2017 (INCB, 2017).

⁽²⁵⁾ NPP known as 1-phenethyl-4-piperidone and *N*-phenethyl-4-piperidone

Due to the typical high potency of fentanils there is a risk of severe poisoning following accidental exposure during their manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substances. Likewise, accidental exposure to the fentanils could pose a risk of poisoning to the public, law enforcement, emergency personnel, as well as medical and forensic laboratory personnel. In addition to exercising extreme caution when handling materials suspected to contain fentanils, personnel should be equipped with appropriate protective equipment. The antidote naloxone should be readily available to personnel in sufficient quantities; training in resuscitation, including the administration of naloxone, should also be available (IAB, 2017; US CDC, 2013; US DEA, 2017)

Ixxviii) Table 2. Methods of synthesis for carfentanil				
Ixix) Method	Ixx) Starting material	Ixxi) Main reagents	Ixxii) Reference	
Ixxiii) Explorative	Ixxiv) methyl 4-[phenyl(propanoyl)amino]piperidine-4-carboxylate	Ixxv) 2-bromoethylbenzene; dimethylacetamide; ethanol; MgSO ₄ ; chloroform; methanol; methylisobutylketone; oxalic acid	Ixxvi) Van Daele et al., 1976	
Ixxvii) 'Janssen' method	Ixxviii) 1-phenethyl-4-piperidone ⁽²⁶⁾	Ixxix) KCN; aniline; acetic acid; H ₂ SO ₄ ; KOH; ethylene glycol; methanol; propionic anhydride	Ixxx) Malaquin et al., 2010	
Ixxxi) Anhydrous Strecker/amide cyclization	Ixxxii) 1-phenethyl-4-piperidone	Ixxxiii) trimethylsilyl cyanide; aniline; acetic acid; chlorosulfonyl isocyanate; methylene chloride; HCl; NaOH; methyl iodide; DMF	Ixxxiv) Feldman & Brackeen, 1990	
Ixxxv) 'Siegfried' method ⁽²⁷⁾	Ixxxvi) 1-phenethyl-4-piperidone	Ixxxvii) Aniline; NaBH ₄ ; propionyl chloride; HCl; NaOH; dichloromethane;	Ixxxviii) Siegfried, n.d.	
Ixxxix) Ugi multicomponent reaction	xc) propionic acid; aniline; 1-phenylethyl-4-piperidone; 1-cyclohexenyl isocyanide	xcii) Acylchloride 10% /methanol; ethylacetate; NaHCO ₃ ; MgSO ₄ ; brine	xcii) Malaquin et al., 2010	
xciii) Radiotracer synthesis	xciv) [¹¹ C]iodomethane, 4-((1-oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid ⁽²⁸⁾	xcv) Dimethylformamide, H ₂ ; palladium-on-charcoal; NaOH	xcvi) Dannals et al., 1985	

⁽²⁶⁾ *N*-phenethyl-piperidone (NPP) can be synthesized from piperidone and phenethyl-tosylate or phenethyl-bromide through a simple SN₂ mechanism (Siegfried, n.d.).

⁽²⁷⁾ A brief description of this method for the synthesis of fentanyl is found in internet (Siegfried, n.d.). It does not describe how the method can be used for the synthesis of carfentanil.

⁽²⁸⁾ The synthesis of this precursor is described in Dannals et al., (1985).

xcvii) Radiotracer synthesis	xcviii) [¹¹ C]methyl triflate; 4-((1-oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid ⁽²⁹⁾	xcix) DMSO, tetrabutylammonium hydroxide; NH ₄ OH	c) Jewett, 2001
ci) <i>t</i> -butyl ester route	cii) 4-((1-oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid ⁽³⁰⁾	ciii) Methanol; H ₂ SO ₄ ; NH ₄ OH; Na ₂ SO ₄ ; methylisobutylketone; oxalic acid dihydrate	civ) Marton et al., 2012
cv) Radiotracer synthesis	cvi) [¹¹ C]methyl triflate; 4-((1-oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid - tetrabutylammonium salt	cvi) Ethanol; NH ₄ OH	cvi) Blecha et al., 2017

Typical impurities encountered in seized and collected samples

Analytical profiles were provided for three carfentanil submissions to the Drug Enforcement Administration Special Testing and Research Laboratory in the United States. Acetylcarfentanil was characterized as an impurity in two exhibits. According to the authors, acetylcarfentanil presumably arises from the clandestine synthesis of carfentanil, similar to that of acetylfentanyl in illicit fentanyl exhibits (Casale, Mallette, & Guest, 2017).

A1.2. Physical/pharmaceutical form

Carfentanil has been seized as a powder and as a liquid (EMCDDA, 2017a) ⁽³¹⁾.

A1.3. Route of administration and dosage

Carfentanil can be administered orally as a powder, as tablets, or as a solution; it can also be administered intranasally or sublingually via spray or snorted (insufflated); inhaled by vaporising e-liquid type solutions ('vaping'); inhaled by smoking or vaporising the 'free base'; administered transdermally, and injected. In view of its high potency, users may also prepare appropriately diluted solutions for intranasal application using nasal sprays.

⁽²⁹⁾ The synthesis of this precursor is described in Jewett (2001).

⁽³⁰⁾ Various routes of synthesis of this precursor is described in Marton et al., (2012).

⁽³¹⁾ A seizure of carfentanil in plant material was reported to the EMCDDA

Limited information is available regarding the dose and the dose regimens of carfentanil. It is not possible to currently discern the 'typical' dosages administered by users. Doses appear to differ depending on factors such as the route of administration, the tolerance of the users, the use of other drugs, and the desired effects. Furthermore, the purity, amount and/or composition of the substance ingested are not typically known by the user. Moreover, the actual composition of the substance may differ over time and different geographical areas. Given the difficulties of collecting such data, it should be used with caution. This issue is further complicated by the fact that carfentanil is mixed with or sold as heroin and other illicit opioids, meaning that users will not be aware that they are using the substance.

A 26-year-old man with a history of polysubstance use obtained 100 mg of carfentanil via a 'dark web' source. He injected approximately 60 µg carfentanil and ingested 4.9 mg of what he believed to be 'clonazepam'. He was found unconscious and with respiratory depression. In the emergency room he was given a total of 4.4 mg of naloxone intravenously resulting in partial arousal and improvement in respiratory rate. Subsequently, he was given a naloxone infusion, initiated at 5 mg/h for 7h until recovery. His blood contained 1.1 ng/mL carfentanil and alprazolam (Shulman et al., 2017).

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

In this section only primary pharmacology is described. Analgesia and sedation are considered the primary pharmacological effects in this report. Safety pharmacology data are summarized in Section D.1.1. As both efficacy and safety were considered in studies with non-laboratory animals, some of these may be mentioned in both the sections on primary pharmacology and safety pharmacology.

Pharmacodynamics

In vitro studies

Carfentanil is a full μ -opioid agonist.

Binding and activity at the opioid receptors has been measured in many studies. These are summarized in Table 3.

Binding studies show a high affinity of carfentanil for opioid receptors, with a high specificity towards the μ opioid receptor. The data presented by Yeaden and Kitchen (1988) appear to be an exception compared to the data reported by others.

Fitzgerald and Teitler made a quantitative autoradiographic analysis of [3 H]carfentanil binding to μ opioid receptors in the rat brain. Thirty-five brain regions were examined for specific [3 H]carfentanil and [3 H]DAMGO binding. The absolute and relative densities of the sites were essentially identical. The highest levels of binding were observed in the 'patch' areas of the striatum. The lowest levels were observed in the cerebellum where no specific binding of either radioligand was observed. Other areas with high levels of binding (>70 fmol/mg tissue equivalent) were striatum (matrix), superior colliculus superficial layer and nucleus accumbens (Fitzgerald & Teitler, 1993).

In order to investigate the receptor interactions of carfentanil in detail [³H]carfentanil was used as a radioligand for labelling receptors in rat and human brain tissue homogenates. [³H]Carfentanil was found to bind saturably and with high affinity ($K_D = 0.08 \pm 0.01$ nM) to membranes prepared from human cortical ($B_{max} = 42 \pm 3$ fmol/mg) and thalamic ($B_{max} = 84 \pm 3$ fmol/mg) tissues and rat cortex ($B_{max} = 82 \pm 4$ fmol/mg) and diencephalon ($B_{max} = 105 \pm 5$ fmol/mg). Association ($1.23 \pm 0.19 \times 10^{10}$ Mol⁻¹ × min⁻¹) and dissociation rate (0.19 ± 0.03 Mol⁻¹ × min⁻¹) constants were determined in human cortical tissues; results from studies in rat cortical, and rat diencephalon tissue homogenates produced similar kinetic rate constants (Titeler et al., 1989).

μ₁-Specificity of carfentanil binding

In rats, the receptor subtype specificity of binding of carfentanil to μ₁ and μ₂ opioid receptor subtypes was studied in brain sections *in vitro* and with PET imaging *in vivo* (Table 4). Receptor subtype-selective inhibition of [¹¹C]carfentanil binding was studied by pharmacologic intervention, using the μ-receptor inhibitor cyprodime or the μ₁-specific inhibitor naloxonazine. *In vitro*, binding to μ₁ occurs with higher (> 100-fold) relative affinity than for μ₂. The apparent affinity to μ receptors, which is just above the nanomolar range, thus consists of a mixture of very high affinity for μ₁ and medium high affinity for μ₂. [¹¹C]Carfentanil binding to μ₂ *in vivo* could not be detected following specific blocking of μ₁. If the results obtained in this study in rats are translatable to the human situation this would mean that previous and future clinical studies employing [¹¹C]carfentanil will be biased to measure μ₁ rather than μ₂ (Eriksson & Antoni, 2015). See Table 4.

cix) **Table 3.** *In vitro* binding and activity of carfentanil at opioid receptors.

cx) Parameter	cx i) μ	cx ii) δ	cx iii) κ	cx iv) μ/δ	cx v) μ/κ	cx vi) Other receptor preparation	cx vii) Comments	cx viii) μ (reference opioid)	cx ix) Reference
cxx) K_i in guinea pig whole brain membranes	cxx i) 0.024 nM	cxx ii) 3.3 nM	cxx iii) 43 nM	cxx iv) 138	cxx v) 1792	cxx vi)	cxx vii) μ -agonist DAGO; δ -agonist DPDPE; κ -agonist: U-69593	cxx viii) 1.2 nM (fentanyl)	cxx ix) Maguire et al., 1992
cx xx) IC_{50} in guinea pig ileum and mouse vas deferens	cx xx i) 0.019 nM	cx xx ii) 17 nM	cx xx iii) 59 nM	cx xx iv) 895	cx xx v) 26000	cx xx vi)	cx xx vii)	cx xx viii) 3.6 nM (fentanyl)	cx xx ix) Maguire et al., 1992
cx l) K_i in SH-SY5Y cells	cx l i) 0.15 nM	cx l ii)	cx l iii)	cx l iv)	cx l v)	cx l vi)	cx l vii) μ -agonist DAGO	cx l viii) 0.39 nM (fentanyl)	cx l ix) Costa et al., 1992
cl) ED_{50} GTPase inhibition	cl i) <0.1 nM	cl ii)	cl iii)	cl iv)	cl v)	cl vi)	cl vii)	cl viii) 1.3 nM (fentanyl)	cl ix) Costa et al., 1992

clx) ED ₅₀ cAMP inhibition	clxi) <0.01 nM	clxii)	clxiii)	clxiv)	clxv)	clxvi)	clxvii)	clxviii) 0.42 nM (fentanyl)	clxix) Costa et al., 1992
clxx) K _i in rat brain homogenate	clxxi) 0.42 nM	clxxii) 0.42 nM	clxxiii)	clxxiv) 1. 09	clxxv)	clxxvi)	clxxvii) μ-agonist DAGO; δ-agonist DPDPE	clxxviii) 3 .3 (fentanyl)	clxxix) Yeaden & Kitchen, 1988
clxxx) IC ₅₀ in rat brain minus cerebellum	clxxxi)	clxxxii)	clxxxiii)	clxxxiv)	clxxxv)	clxxxvi) 0. 093 nM	clxxxvii) [³ H]fentan yl	clxxxviii) 2 .7 nM (fentanyl)	clxxxix) Leyse n et al., 1977
cxc) IC ₅₀ in rat forebrain	cxci)	cxcii)	cxciii)	cxciv)	cxcv)	cxcvi) 0.17 nM	cxcvii) [³ H]sufentanil	cxcviii) 7.9 nM (fentanyl; 27 nM (morphine)	cxcix) Leysen & Gommeren, 1986
cc) K _i in cloned human opioid receptor	ccci) 0.07 nM	ccii)	cciii)	cciv)	ccv)	ccvi)	ccvii) μ-agonist DAMGO	ccviii) 2.1 nM ([¹⁸ F]fentanyl)	ccix) Henriksen et al., 2005
ccx) K _i in human prefrontal cortex homogenate	ccxi)	ccxii)	ccxiii)	ccxiv)	ccxv)	ccxvi) 0.1 nM	ccxvii) [³ H]carfentanil	ccxviii) 1.4 nM (morphine), 2.4 nM (naloxone)	ccxix) Titeler et al., 1989

ccxx) K_i in rat frontal cortex homogenate	ccxxi)	ccxxii)	ccxxiii)	ccxxiv)	ccxxv)	ccxxvi) 0.1 nM	ccxxvii) $[^3H]$ carfen tanil	ccxxviii) .7 nM (morphine), 5.5 nM (naloxone)	3 ccxxix) Titeler et al., 1989
ccxxx) IC_{50} in rat brain homogenate (2 sites, biphasic kinetics)	ccxxxi) 0.006 & 0.087 nM	ccxxxii) 0.74 & 40 nM	ccxxxiii) 0.008 & 0.125 nM	ccxxxiv)	ccxxxv)	ccxxxvi)	ccxxxvii) μ -agonist DHM; δ -agonist DADLE; κ -agonist: EKC	ccxxxviii)	ccxxxix) Thompson et al., 1987
ccxl) IC_{50} in rat brain homogenate	ccxli) 0.2 nM	ccxlii)	ccxlili)	ccxliv)	ccxlv)	ccxlvi)	ccxlvii) $[^3H]$ naltrexone	ccxlviii) 7 nM (morphine); 25 nM (fentanyl)	2 ccxlix) Maryanoff et al., 1982
ccl) IC_{50} in rat forebrain homogenate	ccli)	cclii)	ccliii)	ccliv)	cclv)	cclvi) 0.089 nM	cclvii) $[^3H]$ fentanyl	cclviii) 2.5 nM (fentanyl)	cclix) Leysen & Laduron, 1978
cclx) EC_{50} rat brain membrane homogenate	cclxi)	cclxii)	cclxiii)	cclxiv)	cclxv)	cclxvi) 72 nM	cclxvii)	cclxviii) .5 nM 3H -etorphine	0 cclxix) Jacobson, 1988

cclxx) Table 4. B _{max} and K _D of [¹¹ C]Carfentanil to rat μ, μ ₁ and μ ₂ receptors from Eriksson & Antoni (2015)						
cclxxi)	cclxxii) Thalamus			cclxxiii) Cortex		
cclxxiv)	cclxxv)μ	cclxxvi) μ ₁	cclxxvii) μ ₂	cclxxviii) μ	cclxxix) μ ₁	cclxxx)μ ₂
cclxxxi) B _{max} (fmol/mg tissue)	cclxxxii) 2.5 ± 10.1 7	cclxxxiii) 6.6 ± 1.6 1	cclxxxiv) 9.6 ± 40.4 8	cclxxxv) 4.9 ± 9.3 6	cclxxxvi) .5 ± 1.2 6	cclxxxvii) 2.8 ± 41.8 9
cclxxxviii) K _D (nM)	cclxxxix) 2.6 ± 4.4 1	ccxc) 0.4 ± 0.4	ccxci) 45.5 ± 30.0	ccxcii) 12.6 ± 4.4	ccxciii) 0.4 ± 0.4	ccxciv) 45.5 ± 30.0
ccxcv) Binding Potential	ccxcvi) 5.8	ccxcvii) 0.2 4	ccxcviii) .0 2	ccxcix) 5.2	ccc) 15.7	ccci) 2.0

In vivo pharmacology studies

The analgesic and sedative effects of carfentanil has been studied in both laboratory animals and non-laboratory animals (Table 5).

cccii) Table 5. Sedative and analgesic activity of carfentanil in laboratory animals							
ccciii) Species ccciv) (N)	cccv) Route	cccvi) Dose	cccvii) Test	cccviij) Endpoint	cccix) Result	cccx) Comments	cccxi) Reference
cccxiij) Rat ♂ Wistar (130)	cccxiij) I V	cccxiv)	cccxv) Tail withdrawal	cccxvi) ED ₅₀	cccxvii) .44 µg/kg	cccxviii) P otency ratio compared to morphine: 7682	cccxi) Van Daele et al., 1976
cccxx) Mouse ♂ Swiss-Webster (10/group)	cccxxi) I V	cccxxii)	cccxxiii) Hot-plate	cccxxiv) D ₅₀	cccxxv) .8 µg/kg	cccxxvi)	cccxxvii) agley et al., 1991
cccxxviii) Rat ♂ Wistar (10/group)	cccxxix) V	cccxxx)	cccxxxii) Tail withdrawal	cccxxxiii) D ₅₀	cccxxxiiii) .37 µg/kg	cccxxxv) T Emax = 15 min; Potency ratio compared to morphine: 10031	cccxxxvi) an Bever et al., 1976
cccxxxvi) Rats S.D. ♂ (5/group)	cccxxxvii) V	cccxxxviii) 0 µg/kg	cccxxxix) Sedation	cccxl) Duration of loss of righting reflex (LORR)	cccxli) 10 min.	cccxlii) Reduction of LORR to 22.69% and 8.46% with 9.4 or 150 µg/kg IM nalmeferene	cccxlili) Song et al., 2014
cccxliv) White albino ICR ♂	cccxlvi) S C	cccxlvi)	cccxlvi) Hot-plate	cccxlviij) D ₅₀	cccxlvi) 0.4 µg/kg	cccxlvi)	cccxlvi) Jacobson, 1988
ccccli) White albino ICR ♂	ccccli) S C	ccccli)	ccccli) Phenyl-quinone writhing test	ccccli) ED ₅₀	ccccli) 0.06 µg/kg	ccccli)	ccccli) Jacobson, 1988
ccccli) White albino ICR ♂	ccccli) S C	ccccli)	ccccli) Tail flick	ccccli) D ₅₀	ccccli) 0.2 µg/kg	ccccli)	ccccli) Jacobson, 1988
ccccli) White albino ICR ♂	ccccli) S C	ccccli)	ccccli) Tail flick	ccccli) D ₅₀	ccccli) 0.2 µg/kg	ccccli)	ccccli) Jacobson, 1988
ccccli) White albino ICR ♂	ccccli) S C	ccccli)	ccccli) Tail flick	ccccli) D ₅₀	ccccli) 0.2 µg/kg	ccccli)	ccccli) Jacobson, 1988

ice albino ICR ♂	C		ilsen ³²		egative		acobson, 1988
ccclxxvi) at ♂ Wistar	ccclxxvii) V	ccclxxviii)	ccclxxix) ail withdrawal	ccclxxx) D ₅₀	ccclxxxi) .6 µg/kg	ccclxxxii) 1 1 µg/kg for fentanyl	ccclxxxiii) eyesen & Laduron, 1978
ccclxxxiv) ew Zealand white rabbit	ccclxxxv) V	ccclxxxvi)	ccclxxxvii) ooth pulp assay	ccclxxxviii) D ₅₀	ccclxxxix) .11 µg/kg	cccxc) 7.4 µg/kg for fentanyl	cccxcii)Wyn n et al., 1986
cccxcii) IV: intravenous; SC: subcutaneous; IM: intramuscular.							

The efficacy of carfentanil as an immobilizing agent for members of *Cervidae* family has been demonstrated in 19 well controlled pivotal and corroborative clinical field trials conducted with 158 moose, 295 elk, 18 Axis deer (*Axis axis*), 9 Sika deer (*Cervus nelsoni*) and 29 exotic *Cervidae* (mainly Indian hog deer (*Hyelaphus porcinus*) and a few pampas deer (*Ozotoceros bezoarticus*), muntjac (*Muntiacus spec.*) and Eld's deer (*Panolia eldii*) (US FDA, n.d.). Based on these data the United States Food and Drug Administration approved Wildnil® for use in *Cervidae*. The recommended dose for use as an immobilising agent in *Cervidae* is 5-20 µg/kg bodyweight, administered in a large muscle mass (US FDA, n.d.).

Based on field trials in South African national parks in more than 200 animals, dose recommendations were made for 19 wild animal species ranging from 1 µg carfentanil/kg bodyweight (African elephant and square-lipped rhinoceros) to 12.5 µg/kg (warthog) (De Vos, 1978).

In addition to these species, carfentanil has also been used for the immobilisation of many other species (Table 6). In the majority of reports carfentanil was administered intramuscularly (IM). Most doses are in the range of 5-20 µg/kg. However, administration by mouth (PO), facilitating transmucosal transport, was reported as well. In these cases carfentanil is readily absorbed transmucosally in the buccal cavity or sublingually. These tissues have a dense vasculature. Reports showing that orogastric administration greatly increases time of onset of sedation and require higher doses support this view (Mortenson, 1994; Walsh & Wilson, 2002). Of note, studies of non-human primates, especially those belonging to the great apes (*Hominidae*) have shown that transmucosal (TM) doses as low as 2 µg/kg can lead to deep sedation of these animals (Kearns et al., 1999; Kearns et al., 2000)

⁽³²⁾ In the Nilsen assay electrical pulsations are given to the mouse tail. A drug is considered active at a given dose level in an individual mouse if that mouse responded consecutively in at least two of the four time periods by vocalisation (Perrine et al., 1972).

The use of carfentanil (usually in combination with the α_2 adrenergic agonist xylazine) has been compared with other anaesthetic drugs or drug combinations such as medetomidine/ketamine, sufentanil, sufentanil/xylazine, telazol/xylazine, detomidine, medetomidine/xylazine/atipamezol, ketamine/xylazine and etorphine/xylazine. In several studies carfentanil showed some disadvantages compared to the comparators, such as longer induction time and larger risk of renarcotisation. The latter may be related to a longer clearance time and/or recirculation from tissue depots.

To reverse the narcosis, naltrexone is most often chosen as antidote for carfentanil, usually in a 100:1 ratio. Lower ratios or the use of naloxone may increase the risk of re-narcotisation. Usually naltrexone was partly administered intravenously (IV) and partly subcutaneously (SC), however, intranasal administration can also be effective. For humans a naltrexone solution is not available and naloxone solutions are used for opioid antagonism (Section 3.4).

cccxciii) Table 6. Sedative activity of carfentanil in non-laboratory animals.					
cccxciv) Spe cies	cccxcvi) oute	cccxcvii) ose (average)	cccxcviii) Result	cccxcix) eference	
cccxcv) (N)					
cd) Grey seals (<i>Halichoerus grypus</i>) (46)	cdi) IM	cdii) 10 µg/kg (range: 4.2-24.9)	cdiii) Variable depth of narcosis (difficulty to administer). Naloxone as antidote (46-177x carfentanil dose). 5% died. Probably narrow safety margin	cdiv) Baker & Gatesman, 1985	
cdv) Impala (<i>Aepyceros melampus</i>) (36)	cdvi) IM	cdvii) 14-17 µg/kg	cdviii) 8.6 min to recumbency. Diprenorphine as antidote.	cdix) Cheney & Hattingh, 1988	
cdx) Common eland (<i>Taurotragus oryx</i>) (6)	cdxi) IM	cdxii) 17 µg/kg + 230 µg/kg xylazine	cdxiii) 4.3 min to recumbency. Naltrexone as antidote (100x carfentanil dose)	cdxiv) Cole et al., 2006	
cdxv) Tibetan yak (<i>Bos grunniens</i>) (16)	cdxvi) IM	cdxvii) 15 µg/kg + 250 µg/kg xylazine	cdxviii) 5-7 min to recumbency. Naltrexone as antidote (100x carfentanil dose)	cdxix) Cushing et al., 2011	
cdxx) Moose (<i>Alces alces</i>) (72)	cdxxi) IM	cdxxii) 7.1 µg/kg + 180 µg/kg xylazine	cdxxiii) 88% complete and 8% partial immobilisation. 6.6 min to recumbency. Naltrexone as antidote (100x carfentanil dose). 6% died.	cdxxiv) Delvaux et al., 1999	
cdxxv) Wood bison (<i>Bison bison athabascae</i>) (107)	cdxxvi) IM	cdxxvii) 0.0-8.8 µg/kg + 54-133 µg/kg xylazine	cdxxviii) Naloxone and low levels of naltrexone (<90x carfentanil dose) permit narcotic recycling. A 125:1 ratio is recommended.	cdxxix) Haigh & Gates, 1995	
cdxxx) North American bison (<i>Bison bison</i>) (26)	cdxxxi) IM	cdxxxii) 0.4 µg/kg + 70 µg/kg xylazine	cdxxxiii) Mean induction time 14.2 min. Naloxone as antidote (≈100x carfentanil dose)	cdxxxiv) Lock & Berger, 1987	

cdxxxv) Rhebok (<i>Pelea capreolus</i>) (6)	cdxxxvi) M	cdxxxvii) 0 µg/kg + 400 µg/kg xylazine	cdxxxviii) 4 min until recumbency.	cdxxxix) oward et al., 2004
cdxl) Desert bighorn sheep (<i>Ovis canadensis nelson</i>) (23)	cdxli) I M	cdxlii) 44 µg/kg + 190 µg/kg xylazine	cdxlili) Induction time 6.3 min. Diprenorphine (299 µg/kg) or naloxone (4 mg/kg) as antidote. 2 sheep died.	cdxliv) Jessup et al., 1985
cdxlv) Tule elk (<i>Cervus elaphus nannodus</i>) (17)	cdxlii) I M	cdxlvii) 19 µg/kg + 235 µg/kg xylazine	cdxlvi) Induction time 9.2 min. Diprenorphine (105 µg/kg) or naloxone (1.03 mg/kg) as antidote. 3 elk died.	cdxlix) Jessup et al., 1985
cdli) Wild horses (<i>Equus caballus</i>) (4)	cdlii) IM	cdliii) 17 µg/kg + 610 µg/kg xylazine	cdliiii) Induction time 8 min. Diprenorphine (27 µg/kg) + naloxone (1.1 mg/kg) as antidote.	cdliv) Jessup et al., 1985
cdlv) Guanaco (<i>Lama guanicoe</i>) (14)	cdlvi) I M	cdlvii) 22-50 µg/kg	cdlviii) Time to recumbency 3.7 min. Naltrexone (100 mg ≈ 1 mg/kg) as antidote.	cdlix) Kares h et al., 1998
cdlx) Chimpanzee (<i>Pan troglodytes</i>) (3)	cdlxi) T M	cdlxii) 2-4 µg/kg	cdlxiii) Deep sedation after 22 minutes. Severe respiratory depression at 25 minutes.	cdlxiv) Kearns et al., 1999
cdlxv) Chimpanzee (<i>Pan troglodytes</i>) (5)	cdlxvi) T M	cdlxvii) 2 µg/kg (after 2.5 mg droperidol PO)	cdlxviii) Naltrexone (100x carfentanil dose)/tiletamine/zolazepam as antidote. Premedication with droperidol diminished respiratory depression.	cdlxix) Kearns et al., 2000
cdlxx) Bonobo (<i>Pan paniscus</i>) (2)	cdlxxi) T M	cdlxxii) 2 µg/kg (after 2.5 mg droperidol PO)	cdlxxiii) Naltrexone (100x carfentanil dose)/tiletamine/zolazepam as antidote. Mild to moderate respiratory depression.	cdlxxiv) earns et al., 2000
cdlxxv) Capuchin monkeys (<i>Cebus apella</i>) (2)	cdlxxvi) M	cdlxxvii) µg/kg	cdlxxviii) Mild sedation ; no respiratory depression.	cdlxxix) earns et al., 1999

cdlxxx)Gibbons (<i>Hylobates lar</i>) (2)	cdlxxxi) M	cdlxxxii) $\mu\text{g/kg}$	cdlxxxiii) Mild to moderate sedation ; no respiratory depression	cdlxxxiv) earns et al., 1999
cdlxxxv) Gemsbok (<i>Oryx gazelle</i>) (6)	cdlxxxvi) M	cdlxxxvii) $1 \mu\text{g/kg} + 116 \mu\text{g/kg}$ xylazine	cdlxxxviii) Time to recumbency 4.1 min. Antidote naltrexone ($\approx 1 \text{ mg/kg}$).	cdlxxxix) ilgallon, Lamberski, & Larsen, 2010
cdxc) Gray wolves (<i>Canis lupis</i>) (2)	cdxci) I M	cdxcii) $7.5 \mu\text{g/kg} + 500 \mu\text{g/kg}$ xylazine	cdxciii) Induction time 8 min.	cdxciv)Kreeger & Seal, 1990
cdxcv) Grizzly bears (<i>Ursus arctos</i>) (7)	cdxcvi)I M	cdxcvii) $1 \mu\text{g/kg} + 120 \mu\text{g/kg}$ xylazine	cdxcviii) Induction time 4.3 min. Antidote: naltrexone $1 \text{ mg/kg} + 2 \text{ mg/kg}$ tolazoline.	cdxcix)Kreeger et al., 2013
d) Black bear (<i>Ursus arctos</i>) (3)	di) IM	dii) $14 \mu\text{g/kg} + 150 \mu\text{g/kg}$ xylazine	diii) Induction time 5.2 min. Antidote: naltrexone $1 \text{ mg/kg} + 2 \text{ mg/kg}$ tolazoline.	div) Kreeger et al., 2013
dv) Alaskan moose calves (<i>Alces alces gigas</i>) (13)	dvi) IM	dvii) $7 \mu\text{g/kg} + 360 \mu\text{g/kg}$ xylazine	dviii) Induction time 4.5 min. Antidote: naltrexone $1.2 \text{ mg/kg} + 2.4 \text{ mg/kg}$ tolazoline	dix) Kreeger & Kellie, 2012
dx) Hartbeest (<i>Alcelaphus buselaphus major</i>) (24)	dxii) IM	dxii) $7-10 \mu\text{g/kg} +$ azaperone or xylazine	dxiii) Induction time 8.5 min	dxiv) Kupper et al, 1981
dxv)Kob (<i>Kobus kob</i>) (16)	dxvi) I M	dxvii) $5-33 \mu\text{g/kg} +$ azaperone or xylazine	dxviii) Induction time 5.3 min. Many animals showed nervous excitement. 2 died.	dxix) Kupper et al, 1981
dxx)Caribou calves (<i>Rangifer tarandus granti</i>) (21)	dxxi) I M	dxxii) $1.5-1.8 \text{ mg/animal} + 20-25 \text{ mg/animal}$ xylazine	dxxiii) Induction time 3.2 min. Naltrexone ($100 \times$ carfentanil dose) as antidote.	dxxiv) Lian et al., 2016

dxxv) White-tailed deer (<i>Odocoileus virginianus</i>) (29)	dxxvi) I M	dxxvii) 7.75–46.84 µg/kg + 0.16–0.27 mg/kg xylazine	dxxviii) dxxix) Initial excitement. Induction time 4.7±3.3 min. Naltrexone (100x carfentanil dose) + yohimbine as antagonist.	dxxx) Miller et al., 2003
dxxxi) White-tailed deer (<i>Odocoileus virginianus</i>) (11)	dxxxii) I M	dxxxiii) 30 µg/kg + 0.3 mg/kg xylazine	dxxxiv) Induction time 3 min. Reversal with naltrexone (3 mg/kg) and yohimbine (0.15 mg/kg). Induction time slightly decreased with addition of ketamine, but quality of anaesthesia decreased.	dxxxv) Storms et al., 2006
dxxxvi) Rocky mountain elk (<i>Cervus elaphus nelsoni</i>) (12)	dxxxvii) I M	dxxxviii) 0 µg/kg	dxxxix) Induction time 3.1 min. Naltrexone administered as 0, 25, 50 or 100 mg/mg carfentanil. Recovery time independent of naltrexone dose. No renarcotisation at 100 mg/mg. 3/8 and 7/9 renarcotised at 50 and 25 mg/mg.	dxi) Miller et al., 1996
dxli) Rocky mountain wapiti (<i>Cervus elaphus nelsoni</i>) (8)	dxlii) I M	dxliii) 10 µg/kg + 0.1 mg/kg xylazine	dxliv) Induction time 3.9 min. Not significantly different when 2 µg naloxone/µg carfentanil was added.	dxlv) Moreasco et al., 2001
dxlvi) Brown bears (<i>Ursus arctos</i>) (5)	dxlvii) P O (mixed in honey)	dxlviii) 6.0–15.2 µg/kg	dxlix) Required dose for anaesthesia: 7.6 µg/kg in winter and 12.7 µg/kg. Sternal recumbency at 7.5 min, complete sedation at 21 min. Antidote naltrexone (100x carfentanil dose). Reversal time 6 min.	dli) Mortenson & Bechert, 2001
dli) Gaur (<i>Bos gaurus</i>) (8)	dlii) IM	dliii) 10 mg/animal + 100 mg xylazine/animal	dliiv) Time to recumbency 4.6 min. 1,000 mg naltrexone and 24 mg yohimbine as antidote.	dlii) Napier et al., 2011
dlvi) Brazilian tapir (<i>Tapirus terrestris</i>)	dlvii) P O (TM)	dlviii) 7.88 µg/kg 20 min after 0.17 µg/kg detomidine (PO)	dliv) Time to recumbency 10.8 min after carfentanil dose. Naltrexone and yohimbine as antidote.	dlx) Pollock & Ramsay, 2003

dlxi) White rhinoceros (<i>Ceratotherium simum</i>)	dlxii) I M	dlxiii) Adult: 1.2 mg/animal	dlxiv) Naltrexone is choice of drug for reversal. Naloxone gives renarcotisation.	dlxv) Portas, 2004
dlxvi) Black rhinoceros (<i>Diceros bicornis</i>)		dlxvii) Juvenile: 0.9 mg/animal; adult: 1-1.5 mg/animal		
dlxviii) Greater one horned rhinoceros (<i>Rhinoceros unicornis</i>) (1)	dlxix)			
dlxx) Ostriches (<i>Struthio camelus</i>) (20)	dlxxi) I M	dlxxii) 3 mg/animal + 150 mg xylazine/animal	dlxxiii) Recumbency after 4.7 min following initial excitement. Reversal with naltrexone (300 mg) and yohimbine (0.125 mg/kg).	dlxxiv) Raath et al., 1992
dlxxv) Himalayan tahr (<i>Hemitragus jemlahicus</i>) (12)	dlxxvi) I M	dlxxvii) 9 µg/kg + 0.08 mg/kg xylazine	dlxxviii) Time to recumbency 4 min. Reversal with naltrexone (867 µg/kg) and atipamezole (105 µg/kg).	dlxxix) Rainwater et al., 2013
dlxxx) Black bears (<i>Ursus americanus</i>) (10)	dlxxxi) P O (mixed with honey)	dlxxxii) 6.8-18.8 µg/kg	dlxxxiii) Time to sternal recumbency 7.7 min. Time to total sedation 19.7 min. Reversal with 100 mg naltrexone/mg carfentanil.	dlxxxiv) Ramsay et al., 1995
dlxxxv) Bongo antelopes (<i>Tragelaphus eurycerus</i>)	dlxxxvi) M	dlxxxvii) 0.3 µg/kg + 0.079 mg/kg xylazine	dlxxxviii) Induction time 6 min. Reversal with Naltrexone (0.82 mg/kg) and yohimbine (0.12 mg/kg)	dlxxxix) Schumacher et al., 1997
dxci) Dama gazelles (<i>Gazella dama</i>) (16)	dxci) I M	dxcii) 18.4 µg/kg	dxci) Induction time 6 min. Reversal with naltrexone (1.8 mg/kg)	dxci) Schumacher et al., 1997

dxcv) Moose (<i>Alces alces</i>) (21)	dx cvi) I M	dx cvii) 3-4 mg/animal + 100-175 mg/animal xylazine	dx cviii) Induction time 4.1 min. No excitement phase evident. 2 animals died.	dx cxix) Seal et al., 1985
dc) White-tailed deer (<i>Odocoileus virginianus</i>)	dc i) IM	dc ii) 14.2 µg/kg carfentanil and 17.8 µg/kg of medetomidine	dc iii) Induction time 13.3 min. 2/16 animals had incomplete narcosis. Reversal with intranasal or intramuscular naltrexone (1.5 mg/kg) and atipamezole (0.1 mg/kg). Both routes were as effective.	dc iv) Shury et al., 2010
dcv) Domestic goats (<i>Capra hircus</i>) (8)	dc vi) b uccal	dc vii) 60 µg/kg + 60 µg/kg detomidine + 0.5% saponin	dc viii) Induction time 22 min after long excitement phase (9.6 min). Reversal with naltrexone (3 mg/kg + yohimbine 0.375 mg/kg or atipamezole	dc ix) Sleeman et al., 1997
dcx) IM: intramuscular; PO: by mouth; TM: transmucosal.				

Human studies

In vivo binding to opioid receptors

Binding of [¹¹C]diprenorphine was compared with [¹¹C]carfentanil binding in the brain of volunteers. This showed that carfentanil had a tenfold higher binding potential as shown by competition with naloxone. The ED₅₀ values were 1.7 and 13 µg/kg respectively. The *in vivo* 'Hill coefficient' of – 1.05 for [¹¹C]carfentanil is consistent with its high selectivity for µ receptors (Villemagne et al., 1994).

The high and specific affinity of [¹¹C]carfentanil for µ opioid receptors has made it an important tool for studying the opioid system with PET imaging in humans. Since the seminal work of Frost and Dannals many research papers have been published where [¹¹C]carfentanil has been used (Dannals et al., 1985; Frost et al., 1985). This literature is not reviewed in this report, but some additional data illustrating tissue and brain distributions are discussed in the pharmacokinetics section on distribution.

Pharmacokinetics

General pharmacokinetics and metabolism

Absorption

Animal data

In female (N=6) common eland (*Taurotragus oryx*), carfentanil was rapidly absorbed after intramuscular (IM) administration of 16.9 µg/kg (co-administered with 0.23 mg/kg xylazine). The mean T_{max} was 13.8 min. Mean plasma $AUC_{0-\infty}$ was 30 ± 5 hr.ng/mL. C_{max} was 13 ± 6.7 ng/mL. In this species carfentanil had a plasma $T_{1/2}$ of 7.7 h (Cole et al., 2006).

In adult (N=8) domestic goats (*Capra hircus*), carfentanil was rapidly absorbed after IM administration of 40 µg/kg. The mean T_{max} was 10.8 min. Mean plasma $AUC_{0-\infty}$ was 11 ± 6.3 hr.ng/mL. C_{max} was 9 ± 5.6 ng/mL. In this species carfentanil had a plasma $T_{1/2}$ of 5.5 h (Mutlow et al., 2004).

Absorption of carfentanil/detomidine (1:1) 60 µg/kg in 0.5% saponin solution (absorption enhancer) after buccal administration was studied in (N=8) domestic goats (*Capra hircus*). Interanimal variability was large with some animals showing peak plasma levels at the first measurement after administration, whereas others showed only gradual and lesser increases of plasma levels (Sleeman et al., 1997).

Other studies investigating the feasibility of administration of carfentanil in the mouth in wild animals indicate that carfentanil is readily absorbed transmucosally (Mortenson & Bechert, 2001; Pollock & Ramsay, 2003; Ramsay et al., 1995), as was also shown for non-human primates (Kearns et al., 1999; Kearns et al., 2000).

Orogastric absorption appears to be much less. Chimpanzees, given 2.0 µg/kg in grapes or pieces of orange, showed minimal, if any, sedative effect. These food items do not appear to promote mucosal contact with the drug efficiently (Kearns et al., 1999). Another study investigated carfentanil administered to gibbons in juice (Mortenson, 1994). Each gibbon was given a mean dose of 381 µg/kg of carfentanil, far more higher than a transmucosal administered dose (mixed with honey) of 2 µg/kg which produced stage 3-4 anaesthesia in this species (Kearns et al., 1999).

While no pharmacokinetic measurements were included by Wong et al., (2017) in a study on the effects of inhaled aerosolized carfentanil on real-time physiological responses in mice, the data show that carfentanil is rapidly absorbed after inhalation, as the mice lost consciousness within one minute after the start of exposure (Wong et al., 2017).

Human data

An aerosolized mixture containing carfentanil and remifentanil and/or halothane allegedly used by Russian military when ending a Chechen hostage in Moscow led to the death of 127 hostages. This also suggests an effective uptake of carfentanil by inhalation (Riches et al, 2012; Stanley, 2003; Wax et al., 2003). For further details see Section D.1.2.

Finally a case report on a veterinarian who had been exposed by splashing of a 1.5 mg carfentanil/50 mg xylazine solution in his face, eyes and mouth, while trying to dislodge a dart from a tree trunk reported that the victim became drowsy within minutes, even when he had washed his face immediately with water. While it is not possible to discern the effects of carfentanil from xylazine in this case, nor the contribution of each route of exposure (dermal/ocular/transmucosal), it appears that carfentanil was readily absorbed (George et al., 2010).

Distribution

Protein binding

In human plasma, fentanyl, sufentanil, alfentanil and lofentanil are 84.4, 92.5, 92.1 and 93.6% protein-bound, respectively (Meuldermans et al., 1982). Based on structural similarity and the lipophilic nature, it may be hypothesized that carfentanil should also be highly bound.

Animal data

Biodistribution was studied in male ddY mice after intravenous injection of 1.11 MBq (5 µg/kg) of [¹¹C]carfentanil. Carfentanil was rapidly cleared from blood. High initial uptake was observed in the lungs, kidneys, and liver, with the radioactivity in the lungs and kidneys clearing rapidly and the radioactivity in the liver increased with time. A good uptake in brain was observed. A brain/blood ratio of 1.5-1.8 was found from 5 to 30 min (Table 7) (Saji et al., 1992).

dcxi) Table 7. Biodistribution of [¹¹ C]carfentanil in mice (% dose/g organ) (from Saji et al., 1992).				
dcxii) Organ	dcxiii) Time (min)			
	dcxiv) 5	dcxv) 15	dcxvi) 30	dcxvii) 60
dcxviii) Blood	dcxix) 2.09 (0.17)	dcxx) 1.79 (0.39)	dcxxi) 1.47 (0.47)	dcxxii) 1.18 (0.14)
dcxxiii) Liver	dcxxiv) 8.53 (0.47)	dcxxv) 9.89 (1.15)	dcxxvi) 9.89 (3.48)	dcxxvii) 12.46 (1.39)
dcxxviii) Kidney	dcxxix) 14.66 (2.82)	dcxxx) 9.03 (2.83)	dcxxxi) 6.97 (1.22)	dcxxxii) 5.88 (0.71)
dcxxxiii) Lung	dcxxxiv) 6.43 (1.86)	dcxxxv) 3.86 (0.89)	dcxxxvi) 2.86 (0.74)	dcxxxvii) 1.90 (0.51)
dcxxxviii) Heart	dcxxxix) 3.91 (0.58)	dcxli) 2.35 (0.31)	dcxlii) 1.83 (0.17)	dcxliii) 1.22 (0.25)
dcxliv) Brain	dcxlv) 3.73 (0.34)	dcxlvi) 2.85 (0.94)	dcxlvii) 2.13 (0.55)	dcxlviii) 1.28 (0.25)
dcxlix) Brain/blood ratio	dccli) 1.79 (0.14)	dcclii) 1.54 (0.42)	dccliii) 1.46 (.027)	dccliv) 1.09 (0.17)

Human data

In a Positron Emission Tomography (PET) scan study, 13 healthy non-drug-using volunteers (25 ± 3.2 years, 46% male, 80% white) received an IV bolus of 19 ± 19 ng/kg [¹¹C]carfentanil. The calculated T_{1/2} was 41.8 ± 17.5 minutes. However, blood samples were collected only during 90 minutes, i.e. in the distribution phase, so that the terminal elimination phase is likely to have been missed (Minkowski et al., 2012).

During studies on the brain uptake of intravenously administered [¹¹C]carfentanil in eight healthy human volunteers, high accumulation of radioactivity were seen in basal ganglia, thalamus, and cortical regions (Hirvonen et al., 2009).

The distribution of [¹¹C]carfentanil was studied in humans (two males and three females) using whole-body PET imaging. The greatest uptake initially was in the liver and subsequently, over the course of the imaging, more radioactivity appeared in the bladder (Newberg et al., 2009). In Table 8 the mean organ-absorbed doses are given.

dcliii) Table 8. Absorbed dose estimates for each organ ($\mu\text{Gy}/\text{MBq}$) (from Newberg et al., 2009).	
dcliv) Organ	dclv) Mean \pm S.D.
dclvi) Urinary bladder wall	dclvii) 36.50 ± 1.84
dclviii) Liver	dclix) 9.68 ± 2.44
dclx) Kidneys	dclxi) 4.26 ± 1.89
dclxii) Gallbladder wall	dclxiii) 4.21 ± 1.11
dclxiv) Brain	dclxv) 3.98 ± 0.96
dclxvi) Uterus	dclxvii) 3.89 ± 0.50
dclxviii) Osteogenic cells	dclxix) 3.22 ± 0.69
dclxx) Spleen	dclxxi) 3.15 ± 1.20
dclxxii) Heart wall	dclxxiii) 3.14 ± 0.57
dclxxiv) Ovaries	dclxxv) 2.98 ± 0.49
dclxxvi) Lower large intestine wall	dclxxvii) 2.96 ± 0.48
dclxxviii) Lungs	dclxxix) 2.93 ± 0.56
dclxxx) Pancreas	dclxxxi) 2.76 ± 0.58
dclxxxii) Small intestine	dclxxxiii) 2.75 ± 0.54
dclxxxiv) Upper large intestine wall	dclxxxv) 2.71 ± 0.54
dclxxxvi) Adrenals	dclxxxvii) 2.69 ± 0.56

dclxxxviii) Red marrow	dclxxxix) 2.54 ± 0.57
dcxc) Stomach wall	dcxci) 2.40 ± 0.51
dcxcii) Testes	dcxciii) 2.33 ± 0.40
dcxciv) Thymus	dcxcv) 2.04 ± 0.43
dcxcvi) Muscle	dcxcvii) 1.99 ± 0.28
dcxcviii) Thyroid	dcxcix) 1.98 ± 0.41
dcc) Breasts	dccli) 1.77 ± 0.39
dccii) Skin	dccli) 1.62 ± 0.34

Regional brain distribution

Animal data

Regional cerebral distribution studies in the mouse show a significantly higher uptake of [^{11}C]carfentanil by the thalamus and striatum than by the cerebellum, with the radioactivity in the striatum disappearing more rapidly than that in the thalamus (Saji et al., 1992).

Regional brain distribution was also studied in the CD-rat and CD-1 mice. Preferential binding compared to cerebellum in the rat was hypothalamus > striatum > thalamus > cortex > hippocampus > pons/medulla. In mice preferential binding was similarly distributed: hypothalamus > thalamus \approx striatum > cortex (Jewett & Kilbourn, 2004).

Human data

The specific binding and cerebral uptake of [^{11}C]carfentanil and its radioactive metabolites in human subjects was studied (Frost et al., 1989; Endres et al., 2003). Depending on the compartmental model used, thalamus or amygdala showed the highest level of binding, with caudate displaying similar binding potential as the amygdala, closely followed by the putamen. Lower levels of binding potential—but still higher than in reference tissue (blood or occipital)—was observed in cingulate, periaqueductal, cerebellum and temporal, frontal and parietal cortex. Using compartmental modelling, it was estimated that [^{11}C]carfentanil-associated radioactivity appeared rapidly in all brain regions (thalamus, cingulate, cerebellum and occipital), but occipital showed a rapid initial clearance (approximately 50% of radioactivity had disappeared within 20 minutes, whereas in regions with higher binding potential radioactivity disappeared more gradually (in thalamus approximately 75% of radioactivity still remained after 90 minutes) (Endres et al. 2003).

Metabolism

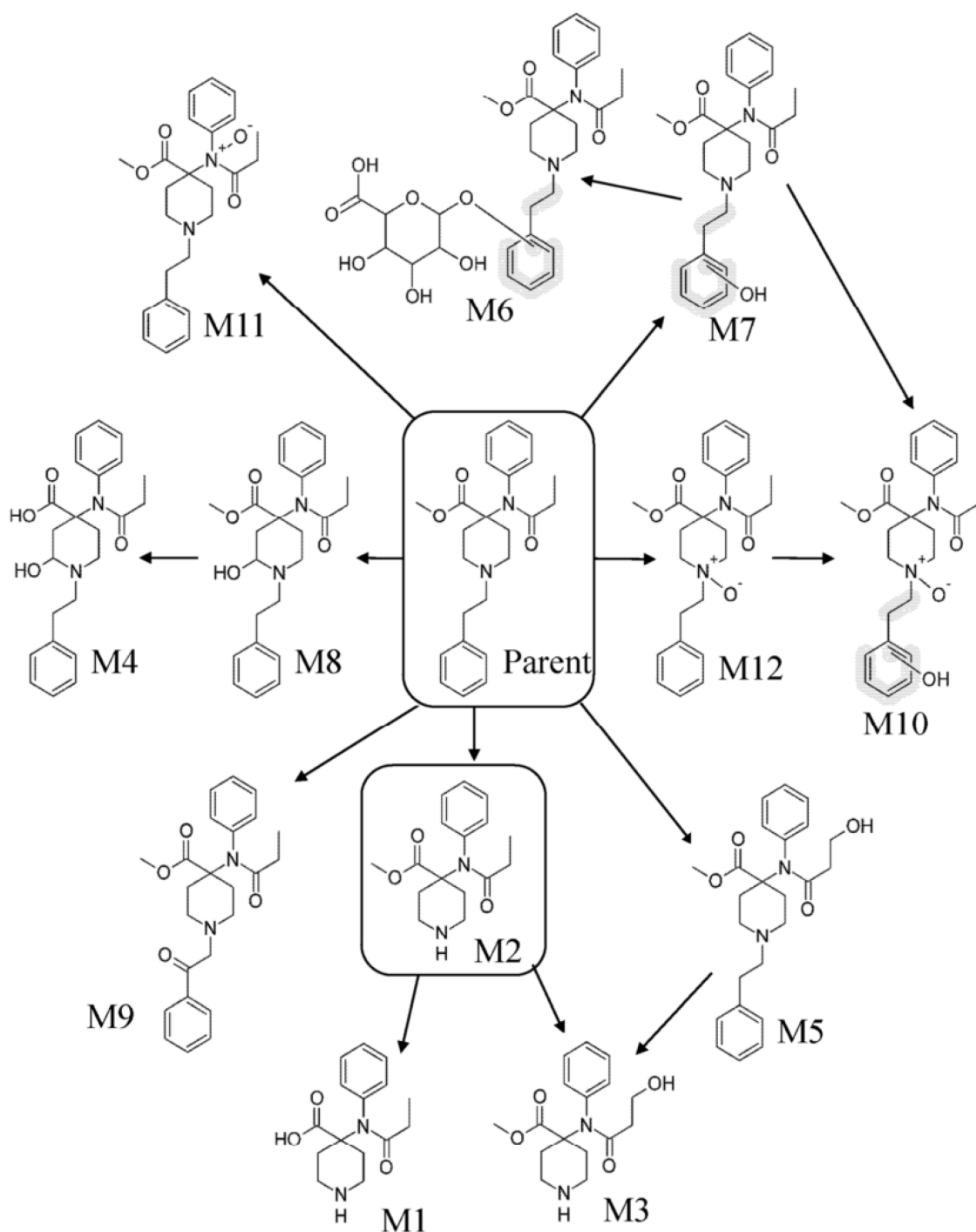
Metabolism of carfentanil was studied in human liver microsomes and hepatocytes. Twelve metabolites were identified. *N*-Dealkylation and monohydroxylation of the piperidine ring were the dominant metabolic pathways, leading to metabolites M2 (norcarfentanil) and M8 (Figure 2), respectively. Two *N*-oxide metabolites and one glucuronide metabolite were observed. Ester hydrolysis was not a major metabolic pathway for carfentanil (Feasel et al., 2016).

Limited information from blood and urine samples from drug users confirms the presence of the major hydroxy metabolite M8, while the hydroxyl metabolite M7 and norcarfentanil are detected as well (Hudson, 2017). Another report confirms the presence of norcarfentanil in serum and urine in a drug user (Müller et al., 2017).

In human liver microsomes, carfentanil half-life was 7.8 min (Feasel et al., 2016). Based on this figure, the authors estimated an *in vivo* intrinsic clearance of 16.2 mL/min/kg. However, when cryopreserved human hepatocytes were used to investigate carfentanil metabolism, carfentanil peak intensity did not decrease significantly over 6 h.

In vivo, rapid metabolism was shown in a study in 6 human volunteers who received a bolus IV injection of [¹¹C]carfentanil (19.0 ± 1.5 mCi carfentanil with a specific activity of 4807 ± 1303 mCi/ μ mole; ≈ 1.5 μ g carfentanil/person). By 40 min post-injection, radioactive metabolites account for more than 50% of the total plasma radioactivity. The main metabolite was more polar than carfentanil and suggested to be norcarfentanil. In addition a more lipophilic metabolite was observed (Endres et al., 2003). In an earlier study in 5 volunteers it was found that after 20 minutes 50% of [¹¹C]carfentanil associated radioactivity in plasma was present as metabolites. After 90 minutes approximately 25% of carfentanil was unmetabolised. In the presence of naloxone carfentanil metabolites appeared 10–15% more rapidly (Frost et al., 1989).

For fentanyl systemic elimination occurs primarily by hepatic metabolism (Labroo et al., 1997). The main metabolic route is *N*-dealkylation mediated by CYP3A4 (Guitton et al., 1997; Labroo et al., 1997; Saari et al., 2008), but CYP3A5 may be of relevance as well (Kuip et al., 2017). Based on its similarity in structure and *N*-dealkylation being a common route of metabolism, it is expected that carfentanil will also be eliminated primarily by hepatic metabolism involving CYP3A4/5.



dcciv)

dccv) **Figure 2.** Proposed metabolic pathway for carfentanil in human hepatocytes. Metabolite structures derived from MS/MS and chromatographic analysis (Feasel et al., 2016).

Excretion

A 16-year-old male patient was found unconscious and analysis of powder found in the patient's belongings was identified as carfentanil. A urine drug screening immunoassay was negative, but analysis with LC-MS/MS showed a urine concentration of 1.3 ng/mL for carfentanil and 0.5 ng/mL for its main metabolite norcarfentanil. This case demonstrates that carfentanil and its main metabolite norcarfentanil are excreted renally. However, calculation of the renal excretion fraction for carfentanil in this case revealed a value of 1.4%. The low value may be related to high protein binding or renal tubular reabsorption (Müller et al., 2017). Based on structural similarity to sufentanil, alfentanil and lofentanil and the lipophilic nature, it may be hypothesized that carfentanil should also be highly bound (Meuldermans et al., 1982). Furthermore, it is reasonable to expect that a significant proportion of the administered dose will be extracted by the liver, as is also suggested by distribution data obtained in mice (Saji et al., 1992) and human volunteers (Newberg et al., 2009). Data obtained in the latter study also show that a large part of radioactivity ultimately appears in the urinary bladder (Newberg et al., 2009).

Inter-individual genetic variability in metabolising enzymes

As mentioned earlier, fentanyl is thought to be mainly metabolized by CYP3A4 (Guitton et al., 1997; Labroo et al., 1997; Saari et al., 2008). Of note, CYP3A5 contributes to CYP3A-dependent drug clearance and thus may lead to changes in fentanyl pharmacokinetics as well (Kuip et al., 2017). As carfentanil is expected to have similar clearance patterns as fentanyl, polymorphisms in CYP3A genes may also be relevant for subjects exposed to carfentanil. Patients with the CYP3A5*3 gene single nucleotide polymorphism (SNP) had about a 2-fold higher fentanyl plasma concentration normalized by measured absorption rate than patients with the wild-type (*1*1) gene polymorphism and the patients with the heterozygous (*1*3) gene polymorphism. The total clearance of fentanyl is also 30–50% lower for the *3*3 group compared to the other two groups, though Barratt and co-workers found no influence of CYP3A5*3 or the recently discovered CYP3A4*22 SNP on serum fentanyl concentrations (Barratt et al., 2014).

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

N-dealkylation is a main route of metabolism for carfentanil in human liver microsomes. As for fentanyl this metabolic step is likely catabolized by CYP3A4 (Guitton et al., 1997; Labroo et al., 1997; Saari et al., 2008), but CYP3A5 may be of relevance as well (Kuip et al., 2017). This opens the possibility for drug-drug interactions, notably by strong inhibitors of CYP3A4. Concomitant exposure to such compounds, e.g. the antimycotic drugs voriconazole, ketoconazole and troleandomycin or the anti-HIV drug ritonavir, could decrease clearance of carfentanil and thus increase plasma exposures (Kuip et al., 2017; Labroo et al., 1997; Saari et al., 2008). For weaker inhibitors this scenario is unlikely, since carfentanil is only present at very low concentrations and remaining CYP3A4 activity would still suffice.

Effects on ability to drive and operate machines

No studies of the effects of carfentanil on the ability to drive and operate machines have been performed. However, it is well established that opioid analgesics, such as fentanyl, impair the mental and physical ability required to drive and operate machines. This effect is likely to extend to carfentanil.

A3. Psychological and behavioural effects

A3.1 Animal data

Animals administered carfentanil for immobilisation often display an initial excitement phase. Such effects were reported in a wide range of species, including ostriches, goats, gaur, rhinoceros, bison, white-tailed deer and black bears (Kock & Berger, 1987; Napier et al., 2011; Portas, 2004; Raath et al., 1992; Ramsay et al., 1995; Shury et al., 2010; Sleeman et al., 1997; Storms et al., 2005). However, not all species display an excitement phase (Mortenson & Bechert, 2001; Seal et al., 1985).

Mice exposed to carfentanil through the inhalatory route (see Section D.1.1) showed restlessness (spinning/flipping/circling), weakened stressor-provoked response and reduced alertness after recovering from sedation throughout a 24-hour post-exposure period (Wong et al., 2017).

A3.1 Human data

No formal studies on the psychological and behavioural effects of carfentanil in humans have been identified.

From the available data, the psychological and behavioural effects of carfentanil share similarities with fentanyl and other opioid analgesics. Dizziness, drowsiness and incoordination have been reported. Other effects common to opioids such as relaxation and euphoria can be expected; at higher doses, sedation and profound intoxication occur.

A study by Baylon and co-workers is of interest though. In this study subjective responses in experienced opioid users (mild to moderate dependence according DSM III-R) to fentanyl and remifentanyl, an ultra-short acting fentanyl analogue, were compared (Baylon et al., 2000). Measurement of pupil diameters as a pharmacodynamic endpoint showed peak activity for remifentanyl within a minute, while pupil diameter was normal after 20 minutes. Fentanyl peak effect on pupil diameter was approximately after 5 minutes and wore off only gradually, with some constriction still present after 3 hours. Both compounds show significant increases in subjective effects compared to a placebo control. Overall fentanyl showed higher AUCs in VAS scores for subjective effects (liking, good and high effect) than remifentanyl. For measures evaluated within 3 minutes of drug administration, remifentanyl peak score for high effect was greater in magnitude than for fentanyl (High VAS [$p = 0.0053$]). Yet, when later time points were evaluated fentanyl scored higher on all subjective endpoints.

Drowsiness/dizziness is a common side effect observed in volunteers participating in PET scan studies who have been administered labelled carfentanil in the lower microgram range (Minkowski et al., 2012).

Discordant experiences regarding the euphorogenic effects of carfentanil have been posted on drug forums (^{21–23}).

A4. Legitimate uses of the product

Carfentanil is used in veterinary medicine as a tranquilising agent in zoological parks and wildlife environments to rapidly incapacitate large animals in order to facilitate veterinary procedures.

(Lust et al., 2011).

Carfentanil was first introduced to the market for veterinary use in 1986 (Stanley et al., 2008). Carfentanil was marketed in the United States under the proprietary name Wildnil[®] and is approved by the United States Food and Drug Administration (US FDA) for use as an immobilising agent in free-ranging or confined members of the family Cervidae (deer (*Cervidae*), elk (*Cervus elaphus*) and moose (*Alces alces*) (US FDA, n.d.).

Commercial production of Wildnil[®] ceased in 2003, and the substance is available only as a compounded dosage form in a concentration of 3 mg/mL, in 10-mL vials (Lust et al., 2011).

There is no information to suggest that carfentanil is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not carfentanil is currently used in the manufacture of a medicinal product.

Besides its use as an immobilising agent in animals, carfentanil is believed to have been used for this purpose in humans. In October 2002, Russian special forces are thought to have used a gas mixture containing carfentanil as part of a counter terrorism operation (Stanley, 2003; Riches et al., 2012; Wax et al., 2003) (see Section D.1.2).

[¹¹C]-Carfentanil is a selective radiotracer for *in vivo* positron emission tomography (PET) imaging studies of the μ -opioid system. It has been widely used for pre-clinical and clinical PET imaging studies since its introduction in the early 1980s (Dannals et al., 1985, Frost et al., 1985). The carfentanil dose administered IV as a tracer varies from less than 1 μ g to 6.9 μ g (Endres et al, 2003; Frost et al., 1989; Hirvonen et al., 2009)

Section B. Dependence and abuse potential

B1. Animal data

In the United States, carfentanil (NIH 10570) has been evaluated for its dependence potential and abuse liability at the University of Michigan (Woods et al., 1988) and the Medical College of Virginia (Aceto et al., 1988), under co-ordination of the National Institutes of Health, Bethesda, Maryland (Jacobson, 1988).

Carfentanil was shown to have a high antinociceptive potency, as shown in Table 5 (Jacobson, 1988). The EC₅₀ for displacement of [³H]-etorphine binding in rat brain membranes was 72 nM. Inhibition of twitch in electrically-driven mouse vas deferens preparations was observed with an ED₅₀ of 0.01 nM, which was antagonised by naltrexone. These data confirm high affinity and agonist activity at μ opioid receptors (Jacobson, 1988; Woods et al., 1988).

In a primary physical dependence (PPD) study, rats received carfentanil for 6 days and then were placed in abrupt withdrawal. No signs of physical dependence were observed (Aceto et al., 1988).

When rats were administered morphine for 6 days and subsequently administered carfentanil, carfentanil could not substitute morphine when rats were evaluated for changes in body weight and behavioural-withdrawal signs (Aceto et al., 1988).

In a primary physical dependence (PPD) test in rhesus monkeys, the animals received carfentanil every 4–6 hr for 30–50 days. They were placed in abrupt withdrawal and challenged with naloxone periodically. No signs of physical dependence were observed (Aceto et al., 1988).

The single-dose suppression (SDS) test determines the ability of a drug to suppress the signs of withdrawal in morphine-dependent rhesus monkeys. Carfentanil showed complete suppression of withdrawal signs in the tested dose range (0.07–0.5 μ g/kg), already showing half maximal suppression of withdrawal at the lowest dose tested. Its potency was considered to be 25000 times the potency of morphine in this regard (Aceto et al., 1988; Jacobson, 1988).

Carfentanil did not precipitate withdrawal signs in morphine-dependent rhesus monkeys (Aceto et al., 1988).

Carfentanil did not induce self-administration in rhesus monkeys trained to self-administer codeine (Aceto et al., 1988).

Carfentanil was not recognised by rhesus monkeys trained to discriminate either the κ opioid receptor agonist ethylketazocine (EKC) or the μ opioid receptor agonist codeine from saline (Aceto et al., 1988).

The data described above show that carfentanil is a very potent analgesic compound able to suppress withdrawal symptoms in morphine-dependent rhesus monkeys, but not in rats. Furthermore, the data suggest that carfentanil does not cause physical dependence in rats or rhesus monkeys, does not induce self-administration and does not generalise with a κ or μ opioid receptor agonist in drug discrimination test in rhesus monkeys. Similarly, it has been shown that rats trained to discriminate fentanyl from saline did not develop tolerance to the discriminative stimulus effects and did not display any withdrawal effects when treated with naloxone or when fentanyl was withheld from the animals (Colpaert et al., 1976).

B2. Human data

Positive subjective effects including euphoria are thought to contribute to the initiation of dependence to μ -opioid agonists. Once dependence has been developed, daily craving and/or dysphoria present in humans prior to drug taking are considered to contribute to the maintenance of dependence. μ -Opioid agonists are known for developing tolerance (Gerrits et al., 2003).

No specific studies investigating dependence potential of carfentanil in humans have been reported.

In the previously mentioned study by Baylon and co-workers, the Cole/ARCI Abuse Potential and POMS scale in opioid users were significantly larger for fentanyl AUCs and peak scores than the corresponding remifentanyl scores (Baylon et al., 2000). The authors suggest that users seeking longer-lasting drug effects might select fentanyl over remifentanyl, but those who prefer briefer, repeated effects might possibly prefer remifentanyl, if it would be available.

Section C. Prevalence of use

Information from seizures, collected and biological samples

Carfentanil was formally notified on 12 February 2013 by the EMCDDA on behalf of Latvia, in accordance with Article 4 of the Council Decision. The Reporting Form details a seizure of 70.139 grams of light yellow powder that was seized on 8 December 2012 by Latvian Police in Riga. 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.

Since then, 8 additional countries (Belgium, Estonia, Germany, Finland, Lithuania, Sweden, the United Kingdom and Norway) have reported detections ⁽³³⁾ of carfentanil (EMCDDA, 2017a). In addition, Austria reported a collected sample containing carfentanil.

⁽³³⁾ 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.)

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.

An increase in detections of carfentanil in Europe has been observed since 2016. Between 2012 and 2015 the substance was only detected in Latvia and Lithuania. It subsequently appeared in the neighbouring countries of Estonia and Finland. In the last 18 months, a further 5 countries have reported detections of carfentanil for the first time (EMCDDA, 2017a).

Information from seizures

A total of 7 Member States reported a total of 801 seizures ⁽³⁴⁾ of carfentanil to the EMCDDA and/or Europol: Estonia (116 cases), Germany (3), Finland (2), Latvia (387), Lithuania (279), Sweden (4) and the United Kingdom (10). At least 209 seizures have been reported for the first 7 months in 2017.

Most of the seizures have been made by Police at street-level, with additional seizures being made in custodial settings. One seizure of 100 grams was made by Customs in Cologne/Bonn airport and reported by Germany.

Since the first detection of carfentanil in 2012, there has been an observed increase in availability of the substance, as seen from the following breakdown of seizures cases by year and country:

- 1 seizure in 2012 (Latvia),
- 27 seizures in 2013 (Latvia and Lithuania),
- 48 seizures in 2014 (Latvia),
- 160 seizures in 2015 (Latvia and Lithuania).
- 345 seizures in 2016 (Latvia, Lithuania, Estonia and Finland)
- 209 seizures in the first half of 2017 (Estonia, Germany, Finland, Latvia, Lithuania, Sweden and the United Kingdom).

⁽³⁴⁾ Many 'seizures' relate to individual case-level data, however, some data provided to the EMCDDA are aggregated at the country level. Data is drawn from the Joint Report Questionnaires and data provided in the bi-annual data gathering (EU EWS progress and final reports) and from individual Reporting forms submitted on an ad hoc basis.

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 grams of 'unadulterated' carfentanil in powder form. In addition to this seizure, 6 seizures, each of which comprising over 100 grams of carfentanil were reported by 4 Member States; as follows:

- Estonia (209.8 grams, seized in April 2017),
- Germany (100 grams reported through Police correspondence in 2017),
- Lithuania (2 seizures of 200 and 138.5 grams, reported in 2016 and 2017, respectively) and,
- United Kingdom (2 seizures of 209 and 150 grams, both in 2017).

Powders

Carfentanil was detected in powder form in a total of 736 cases that amounted to nearly 3.3 kg of seized material: Estonia (110 cases), Germany (2), Finland (2), Latvia (383), Lithuania (226), Sweden (3) and the United Kingdom (10).

In 224 of these seizures, carfentanil was the only substance reported. In 279 seizures, carfentanil was detected in mixture with heroin. In these cases, in addition to heroin, other substances detected were: cocaine, caffeine, paracetamol, levamisole and phenacetin (4 cases), methadone (3), acryloylfentanyl (3), alpha-PHP (2) and caffeine and paracetamol (1).

Excluding heroin, carfentanil has also been detected in mixtures with a number of opioids. These include: fentanyl (81 cases), methadone (17), fentanyl and furanylfentanyl (10), fentanyl and acryloylfentanyl (7), furanylfentanyl (4), tramadol (3) and acryloylfentanyl (2).

Other combinations include: 12 seizures where carfentanil was found mixed with the synthetic cathinone alpha-PHP; 1 seizure, mixed with the synthetic cannabinoids AM-2201 and XLR-11, and in 1 seizure, mixed with diazepam.

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 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.

Other physical forms

In 53 cases, no information on the physical form was reported. These amounted to over 136 grams and 0.5 ml of material seized.

Purity

The quantification of carfentanil is not routinely performed; however, Lithuania provided information on the purity of carfentanil for 44 analysed samples. In 25 of the cases, heroin was also detected and the relative concentrations of both substances were provided.

In these cases, the purity ranged from 0.00034 to 0.13% carfentanil ⁽³⁵⁾ (mean: 0.043%; median: 0.04%). Thirty seven of the cases (86%) were in the range of 0.03-0.09% purity.

In addition, the concentration of heroin was reported for 63 of the samples that contained carfentanil, with a significant inter-variation found between samples, ranging from 0.008 to 23.9% pure heroin.

Information from collected samples

A total of 4 collected samples were reported to the EMCDDA by 4 countries: United Kingdom (2 cases), Belgium (1) and Norway (1) (EMCDDA, 2017a). In addition, Austria reported a collected sample containing carfentanil.

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

⁽³⁵⁾ One very small sample was reported as 'pure' carfentanil, amounting to 0.00002 grams. This was considered as an outlier and, therefore, it was not included in the calculation.

The sample reported by Belgium was recovered from the scene of a death (apparent suicide), where a small quantity of powder (approximately 0.005 grams), was identified as carfentanil.

The sample reported by Norway was also recovered from the scene of a death. The powder was in a plastic bag labelled 'C.50'.

Information from biological samples

Serious adverse events with confirmed exposure to carfentanil from biological samples are discussed in Section D.

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

Availability, supply, price

Information on production

The United Kingdom reported that there are indications that carfentanil has been shipped from predominantly China/Hong Kong.

Information on 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.

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 (caffeine, paracetamol) before being used or sold on.

Additionally, the National Crime Agency in the United Kingdom reported that they identified a supplier of carfentanil who was using the darknet to advertise and distribute carfentanil both nationally and internationally.

Availability from Internet vendors

The available data shows that carfentanil is sold both on the surface web and on the darknet. A structured search of online vendors on the surface web by the EMCDDA, as well as information from acute intoxications, law enforcement seizures and collected samples suggests that on the surface web the substance is sold as a 'research chemical' or/and as a 'pharmaceutical intermediate'⁽³⁶⁾. In the websites identified, carfentanil was typically sold as a powder, in amounts ranging from 0.1 grams to 3 kg.

Prevalence of use

No studies were identified that have investigated the prevalence of use of carfentanil in the general population. Given its pharmacology and that it is sold openly as a replacement to illicit opioids, it would be expected that those looking for substitutes for opioids may seek out carfentanil and other fentanils. This group includes individuals who use illicit opioids such as heroin and/or prescription opioids to self-medicate with the aim of alleviating pain and/or opioid withdrawal. It also appears that there is interest in this substance by some psychonauts. Overall, the available information does not suggest wide use of the substance.

Data from law enforcement seizures and death investigations confirm 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, many users will not be aware that they are using carfentanil.

Data 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 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, 2017b).

⁽³⁶⁾ The search for online vendors of carfentanil on the surface web was performed on 10/07/2017 using previously established methodology (EMCDDA, 2017b). The search identified 11 vendors that appeared to be based in, and/or claimed to have presence in China (n=5), the United States (n=2), Algeria (n=1) and Turkey (n=1); for the remaining site there was no apparent location mentioned. Seven of the sites listed quantities and prices for carfentanil. The remaining four sites only provided prices on request.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

Safety pharmacology

Safety pharmacological parameters have been studied both in laboratory animals and immobilized non-laboratory animals. These data are summarized in Table 9. The administration of carfentanil in non-laboratory animals may induce excitement and erratic behavior (see also Table 5). This effect may partially be induced by the darting of the animals, but could also be pharmacologically related. The sensitivity to induction of excitement seems to differ between species. For example in a report on the use of carfentanil in kob, many animals showed excitement, whereas in a study in moose it was reported that animals did not show excitement (Kupper et al., 1981; Seal et al., 1985). The extent of excitement may also be influenced by the co-administration of other drugs.

A common effect observed in many species is hypoventilation, which may cause hypoxemia, and acidosis. Heart rate in many studies not affected, but can also be increased or decreased. Arrhythmias have also been observed. The co-administration of other compounds (in most cases xylazine) complicates the interpretation of the cardiovascular effects. In addition the arousal due to the hunt and the darting is a confounding factor. Hyperthermia may be observed, but generally body temperature is unaffected.

dccvi) Table 9. Safety pharmacological effects of carfentanil in animals.					
dccvii)	Species	dccix) Route	dccx) Dose	dccxi) Results	dccxii) Referen ce
dccviii)	(N)				
dccxiii) Chimpanzee (<i>Pan trochodytes</i>) (3)		dccxiv) TM	dccxv) 2-4 µg/kg	dccxvi) deep sedation after 22 minutes. Severe respiratory depression at 25 minutes.	dccxvii) Kearns et al., 1999
dccxviii) Bonobo (<i>Pan paniscus</i>) (2)		dccxix) TM	dccxx) 2 µg/kg (after 2.5 mg dropiderol PO)	dccxxi) Mild to moderate respiratory depression.	dccxxii) Kearns et al., 1999
dccxxiii) Western lowland gorillas (<i>Gorilla gorilla</i>) (2)		dccxxiv) TM	dccxxv) 14 µg/kg (after 1.75 mg dropiderol PO)	dccxxvi) Respirator y arrest 10-12 min after carfentanil dose, followed by cardiac arrest ⁽³⁷⁾	dccxxvii) Kearns et al., 1999
dccxxviii) Mule deer (3) and mule deer/white-tailed deer hybrids (4)		dccxxix) IM	dccxxx) 10 µg/kg +0.3 mg/kg xylazine	dccxxxi) Blood pH↑; base excess↑; hypoventilation; hypoxemia; Ventricular premature contractions, atrial premature contractions, and a junctional escape rhythm; hyperthermia	dccxxxii) Caulkett, Cribb, & Haigh, 2000
dccxxxiii) Impala (<i>Aepyceros melampus</i>) (36)		dccxxxiv) IM	dccxxxv) 14 -17 µg/kg	dccxxxvi) Hyperther mia; cortisol↑ (darting- evoked excitement);	dccxxxvii) Cheney & Hattingh, 1988
dccxxxviii) Mice ♂ Balb/c		dccxxxix) IM	dccxli) 3 µg/kg + 15 mg/kg etomidate	dccxlii) HR↓; Parterial↓; RR↓;	dccxlii) Erhardt et al., 1984
dccxlili) Rhebok (<i>Pelea capreolus</i>) (6)		dccxliv) IM	dccxlv) 10 µg/kg +400 µg/kg xylazine	dccxlvi) RR↓; No significant changes in HR; hypoxemia; glucose↑	dccxlvi) Howard et al., 2004

⁽³⁷⁾ This experiment concerns elective euthanasia.

dcclxviii) Chimpanzee (<i>Pan troglodytes</i>) (5)	dcclxlix) TM	dccl) 2 µg/kg (after oral dropiderol)	dccli) RR↓; PaCO ₂ ↑; pH↓	dcclii) Kearns et al., 2000
dccliii) Gray wolves (<i>Canis lupis</i>) (2)	dccliv) IM	dcclv) 7.5 µg/kg + 500 µg/kg xylazine	dcclvi) Transient tachypnea followed by RR↓	dcclvii) Kreeger & Seal, 1990
dcclviii) Grizzly bear (<i>Ursus arctos</i>) (7)	dcclix) IM	dcclx) 11 µg/kg + 120 µg/kg xylazine	dcclxi) RR↓; hypoxemia	dcclxii) Kreeger et al., 2013
dcclxiii) Black bear (<i>Ursus arctos</i>) (3)	dcclxiv) IM	dcclxv) 14 µg/kg + 150 µg/kg xylazine	dcclxvi) RR↓; hypoxemia	dcclxvii) Kreeger et al., 2013
dcclxviii) Caribou calves (<i>Rangifer tarandus granti</i>) (21)	dcclxix) IM	dcclxx) 1.5-1.8 mg/animal + 20-25 mg/animal xylazine	dcclxxi) Hypoxemia; hypercapnia; lactate↑; body temperature↑	dcclxxii) Lian et al., 2016
dcclxxiii) White-tailed deer (<i>Odocoileus virginianus</i>) (29)	dcclxxiv) IM	dcclxxv) 7.7 5–46.84 µg/kg + 0.16–0.27 mg/kg xylazine	dcclxxvi) Rectal T↑ but during anaesthesia gradual ↓. HR, RR and SpO ₂ normal.	dcclxxviii) Miller et al., 2003
dcclxxix) White-tailed deer (<i>Odocoileus virginianus</i>) (13)	dcclxxx) IM	dcclxxxi) 15–45 µg/kg + 0.15–0.45 mg/kg xylazine	dcclxxxii) Median optimal dose was 30 µg/kg + 0.3 mg/kg xylazine. At this dose induction time was <3.0 min and PaCO ₂ <60 mmHg.	dcclxxxiii) Storms et al., 2005
dcclxxxiv) White-tailed deer (<i>Odocoileus virginianus</i>) (11)	dcclxxxv) IM	dcclxxxvi) 30 µg/kg + 0.3 mg/kg xylazine	dcclxxxvii) Compared to carfentanil/xylazine alone, ketamine caused: PaCO ₂ ↑; blood pH↓; frequency of hyperthermia (>41 °C) increased.	dcclxxxviii) Storms et al., 2006

dcclxxxix) Rocky mountain wapiti (<i>Cervus elaphus nelsoni</i>) (8)	dccxc) IM	dccxci) 10 µg/kg + 0.1 mg/kg xylazine	<p>dccxcii) Hypoxemia ; Arterial pH↓; HR↓; ECG tracings consistent with S-T segment depression, occasional premature ventricular contractions, and short episodes of ventricular tachycardia.</p> <p>dccxciii) Naloxone (2 µg/µg carfentanil) reversed hypoxemia increased arterial pH and RR.</p>	dccxciv) Moresco et al., 2001
dccxcv) Brown bears (<i>Ursus arctos</i>) (5)	dccxcvi) PO (mixed in honey)	dccxcvii) 6.0 -15.2 µg/kg	dccxcviii) hypoventilation and respiratory acidosis.	dccxcix) Mortenson & Bechert, 2001
dccc) Black bears (<i>Ursus americanus</i>) (10)	dccci) PO (mixed with honey)	dcccii) 6.8-18.8 µg/kg	dccciii) Hypoxemia, hypoventilation	dccciv) Ramsay et al., 1995
dcccv) Bongo antelopes (<i>Tragelaphus eurycerus</i>) (8)	dcccvii) IM	dcccvii) 8.3 µg/kg + 0.079 mg/kg xylazine	dcccviii) Hypoxemia ; RR↓; HR↓; Parterial↑; plasma norepinephrine↑; plasma DOPAC↓; Body T normal.	dccvix) Schumacher et al., 1997
dcccix) Dama gazelles (<i>Gazella dama</i>) (16)	dcccxi) IM	dcccxi) 18.4 µg/kg	dcccxi) Induction time 6 min. HR↓; RR↓; blood pressure normal; Body T normal; blood glucose↑.	dcccxi) Schumacher et al., 1997
dcccxi) Domestic goats (<i>Capra hircus</i>) (8)	dcccxi) Bucal	dcccxi) 60 µg/kg + 60 µg/kg detomidine + 0.5% saponin	dcccxi) Bradycardia; Parterial↓;	dcccxi) Sleeman et al., 1997
dcccxi) Rats S.D. ♂ (5/group)	dcccxi) IV	dcccxi) 20 µg/kg	dcccxi) RR↓. Nalmefene reversed hypoventilation more effective than naloxone.	dcccxi) Yong et al., 2014
dcccxi) IM: intramuscular; PO: Oral; TM: transmucosal.				

Sensitivity to carfentanil-induced adverse respiratory effects in non-human primates

The observations made by Kearns at co-workers in non-human primates listed in Table 6 and Table 9 are of interest. Compared to most other species listed, the dose administered is fairly low (2 µg/kg), also considering that the route of administration was transmucosal. Nevertheless chimpanzees developed severe respiratory depression within 25 minutes, shortly after reaching deep sedation (unresponsive to noxious stimuli) and needed immediate rescue with naltrexone. A tenfold higher dose was administered to gorillas for elective euthanasia, which was achieved within 12 minutes (Kearns et al., 1999). Bears receiving similar doses as the gorillas either transmucosally or IM did show hypoventilation and hypoxemia and needed oxygen supply, but did survive (Kreeger et al., 2013; Mortenson & Bechert, 2001; Ramsay et al., 1995). Deer received even higher doses i.m, but did not react with respiratory distress (Miller et al., 2003; Storms et al., 2005; Storms et al., 2006). This shows that the sensitivity to the adverse respiratory effects of carfentanil differs greatly between species. Even between primate species differences are observed, since gibbons and capuchin monkey only had mild to moderate sedative effects and no respiratory depression after a transmucosal dose of 2 µg/kg, whereas in chimpanzees, bonobos and gorillas, three species belonging to the great apes (*Hominidae*), this dose caused deep sedation and respiratory depression, or a tenfold dose was effective in order to euthanize the animals (Kearns et al., 1999).

Physiological responses in mice after inhaled aerosolized carfentanil exposure

The Biochemistry and Toxicology Branch of the US Army Medical Research Institute of Chemical Defence in the United States examined the real-time exposure–response effects of inhaled aerosolized carfentanil on opioid-induced toxicity, respiratory dynamics and cardiac function in mice (Wong et al., 2017). Unrestrained, conscious male CD-1 mice (25–30 g) were exposed to 0.4 or 4 mg/m³ of aerosolized carfentanil for 15 min (Ct = 6 or 60 mg.min/m³) in a whole-body plethysmograph chamber. Minute volume (MV), core body temperature (T_c), mean arterial blood pressure (MAP) and heart rate (HR) were evaluated in animals exposed to carfentanil or sterile H₂O. Loss of consciousness and Straub tail were observed within 1 min following initiation of exposure to 6 or 60 mg.min/m³ of carfentanil. Based on the measured minute volume (43 mL/min) and a bodyweight of 25–30 g, the total inhaled dose equals 8.6–10.3 and 86–103 µg/kg for the low and high dose groups, respectively.

Clinical signs of opioid-induced toxicity were observed in a dose-dependent manner: dyspnoea/laboured breathing; lack of grooming; piloerection; ocular protrusion; abdominal bloating; urinary incontinence; rectal prolapse; ataxia; restlessness (spinning/flipping/circling); weakened stressor-provoked response; and, reduced alertness. Dyspnoea/laboured breathing was severe in both dose groups and observed both during the exposure period and 24 hours after. However, mortality was not observed. The reasons for a lack of mortality are unclear according to the authors, but could be related to species-dependent differences in metabolism, pharmacokinetics/pharmacodynamics, physiology and anatomy.

Exposure to 6 or 60 mg.min/m³ of carfentanil resulted in significant decrease in MV as compared to the controls. MAP, HR and T_c decreased 24h in animals exposed to either 6 or 60 mg.min/m³ of carfentanil as compared to the controls. Post-exposure administration of naloxone (0.05 mg/kg, IM) did not increase the MV of animals exposed to carfentanil to control levels within 24 h, but decreased clinical signs of opioid-induced toxicity and the duration of respiratory depression.

Acute toxicity

The IV LD₅₀ of carfentanil in rats was determined as 3.39 mg/kg. This is 10594 times the ED₅₀ for analgesic potency as measured in the rat tail withdrawal test (Van Bever et al., 1976). In this study, the LD₅₀ value for morphine and fentanyl were 223 and 3.05 mg/kg, respectively.

The acute, metabolic, and neurological effects of 8 opioids ranging in analgesic potency (not including carfentanil) was investigated in dogs by de Castro and coworkers (de Castro et al., 1979a, 1979b, 1979c). A general trend towards metabolic acidosis and hypermetabolism was noticed but important differences appeared according to the drugs and doses chosen. The safety margin for metabolic toxicity (ratio between IV doses producing severe metabolic side-effects and doses necessary for deep surgical analgesia) were calculated for each narcotic and found as follows: 1 for pethidine, 3.3 for piritramide, 13 for morphine and phenoperidine, 12.5 for alfentanil, 60 for fentanyl, 800 for sufentanil and 4 000 for lofentanil (R 34 995). Co-administration of other drugs may decrease or increase the metabolic safety margin of the narcotics. Beneficial associations with morphinomimetics are found with droperidol, etomidate and flunitrazepam (de Castro et al., 1979c). Comparing the IV doses producing severe convulsions with the doses necessary for deep surgical analgesia a safety margin of neurological toxicity was calculated. This was 2.2 for pethidine, 6.6 for piritramide, 16 for phenoperidine, 62.5 for alfentanil, 72 for morphine, 160 for fentanyl, 1,000 for sufentanil, and 10,000 for lofentanil (R 34 995). The authors conclude that for 'pure' narcotics there exists an inverse relationship between analgesic potency and neurological toxicity (de Castro et al., 1979b).

Safety margins as described in the previous paragraphs can be referred to in the literature as a therapeutic index. A high therapeutic index is often interpreted as a margin of safety. However it should be noted it is derived from data obtained in animal studies, not human studies. As discussed above, great apes (*Hominidae*) are far more sensitive to carfentanil-induced respiratory depression and arrest than rodents.

In a study in 3 domestic horses (*Equus spec.*), 10-15 µg/kg carfentanil and 1 mg/kg xylazine administered IM caused muscle fasciculations, running motions and excitement followed by fore limb rigidity, tachycardia, hypertension, increase of rectal temperature and one horse had serosanguinous fluid dripping from a nostril. After administration of naltrexone or naloxone, muscle rigidity decreased and respiratory rate increased. Haemoconcentration and mild acidosis was evident and the horse with serosanguinous fluid dripping had tachypnea. After deterioration of the condition the horse was euthanized. Postmortem investigation showed peribronchial and myocardial edema and severe pulmonary edema (Shaw et al, 1995). Carfentanil/xylazine (20µg/kg:1-2 mg/kg) has been used successfully in Przewalski horses, but muscle contractions, fasciculations, tachycardia and mild hypotonia and hyperthermia were also observed. The reasons why severe adverse reactions occurred in these domestic horses is unknown (Shaw et al. 1995).

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of carfentanil and/or its metabolites in humans.

The available non-clinical *in vitro* pharmacodynamic data on carfentanil suggests some functional similarity to morphine and fentanyl, which also suggests that some toxicological similarity might exist with other opioid analgesics (Moffat et al., 2016). The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, miosis, and respiratory depression or arrest. They are also known to display abuse liability and dependence potential (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; Romberg et al., 2003).

Similar to other opioid analgesics, the most serious acute health risk associated with carfentanil use is rapid and profound respiratory depression, which can lead to apnoea, respiratory arrest and death (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; White & Irvine, 1999). This risk may be greater due to: the difficulty in diluting the substance; 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); a lack of 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.

The antidote naloxone can reverse acute poisoning caused by carfentanil (Kim and Nelson, 2015, Ujváry et al., 2017). Recent clinical and community experience in treating poisonings caused by fentanils suggests that larger than normal doses and repeated doses of naloxone may be required to manage poisoning in some cases; longer periods of observation may also be required (Klar et al., 2016; Moss et al., 2017; Somerville et al., 2017; Sutter et al., 2017). (Section D3.4.)

Data from serious adverse events associated with carfentanil are discussed below. Based on the data reported, the clinical features presented in cases of intoxication involving carfentanil appear to be similar to those found with fentanyl and other opioid analgesics. These included unconsciousness or reduced level of consciousness and respiratory depression or arrest.

Acute intoxications reported by the Member States

In total, 3 acute intoxications with confirmed exposure to carfentanil were reported to the EMCDDA by France (2 cases) and Lithuania (1). The cases occurred in November 2016, January 2017, and May 2017 ⁽³⁸⁾.

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 hospitalisation of the patients. Naloxone was administered to the 3 patients; in at least 2 cases more than one dose was administered 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 patients survived.

⁽³⁸⁾ In addition, France also reported an acute intoxication with suspected exposure to carfentanil. This case is not discussed further in this report.

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, the patient believed that they were taking carfentanil.

Acute intoxications identified from other sources

Mild symptoms as reported in PET scan studies

Minkowski and colleagues studied the potential differential responses to IV [¹¹C]carfentanil in chronic cocaine users and health controls (Minkowski et al., 2017). Healthy controls (N=15) participating in PET scan study received an average IV bolus injection of 0.049 µg/kg (range 0.025-0.069) [¹¹C]carfentanil just at the start of the PET scan. The subjects were regularly asked to score whether they experienced any of five common physical symptoms commonly reported during clinical use of opioid analgesics (itching, nausea, headache, vomiting, and dizziness). During the scan 6.7% reported itching, 33.3 % nausea, 6.7 % vomiting, 60.0% dizziness and 0% headache. Ninety minutes after the scan, 0 % reported itching, 26.7 % nausea, 20.0 % vomiting, 60.0% dizziness and 0% headache. Of note, scores for dizziness and total symptom count during the scan were significantly lower for experienced cocaine users. Ninety minutes after the scan, the cocaine users scored significantly less for nausea, dizziness, any symptom and total symptom count compared to non-cocaine users. Cocaine users (N=23) participating in PET scan study received an average IV bolus injection of 0.045 µg/kg (range 0.011-0.075) [¹¹C]carfentanil just at the start of the PET scan. During the scan 0.0% reported itching, 17.4 % nausea, 0.0 % vomiting, 21.7% dizziness and 4.3% headache. Ninety minutes after the scan, 0 % reported itching, 4.3 % nausea, 4.3 % vomiting, 8.7% dizziness and 4.3% headache (Minkowski et al., 2012).

Accidental intoxications in veterinary use

Cases of human exposure to veterinary injectable anaesthetics were reviewed following a literature search and completion of an online questionnaire (Haymerle et al., 2010). Only one case of carfentanil intoxication was reported. A similar—perhaps the same—case was also separately reported (George et al., 2010). Haymerle and co-workers describe sedation, decreased respiratory and heart rate, dizziness, nausea, alcohol-like intoxication, abnormal behaviour, incoordination, ataxia and hypotension as clinical symptoms. Naltrexone was administered as antidote. On arrival to the emergency department 1 hour later, the patient appeared well and complained only of mild and transient chest discomfort. His vital signs were as follows: temperature, 36.8°C; blood pressure, 134/88 mm Hg; heart rate, 75 bpm; respiratory rate 18 breaths per minute; and 98% oxygen saturation on room air. On examination, his face appeared flushed. Pupils were normal in size and reactive. His heart, lung, abdominal, and neurologic examinations were normal. The electrocardiogram, complete blood count, basic metabolic profile, and cardiac markers were within normal limits. The patient was observed for 24 hours, remained asymptomatic, and was discharged home in stable condition (George et al., 2010). The interpretation of the role of carfentanil in this case is complicated by the co-exposure to xylazine.

On 26 October 2002, Russian military special forces used an incapacitating ‘gas’ in a counter terrorism operation to overthrow Chechen rebels holding hostages at the Moscow Dubrovka Theater Center. Of the 800 hostages in the theater, 127 (16%) died, and more than 650 of the survivors required hospitalization. According to attending physicians, ‘many patients had classic signs of opioid intoxication: pinpoint pupils, unconsciousness, and depressed breathing’. The opioid hypothesis was supported by reports from Russian physicians that naloxone was successful in reversing the effects of the intoxication. The Russian Health Minister announced 4 days after the event that, ‘a fentanyl derivative was used to neutralize the terrorists’ (Wax et al., 2003). It was speculated that the fentanyl derivative concerned could have been carfentanil (Stanley, 2003; Wax et al., 2003). Many years after the incident, LC-MS-MS analysis of extracts of clothing from two British survivors, and urine from a third survivor provided evidence that the aerosol comprised a mixture of two fentanils: carfentanil and remifentanil (Riches et al., 2012). These authors conclude that ‘This account suggests that carfentanil exposures may cause severe intoxication or fatality in the absence of prompt and appropriate medical treatment. The same conclusion can be drawn for remifentanil. Both carfentanil and remifentanil have narrow safety margins, meaning that potentially fatal side effects, including respiratory depression, can occur at doses only slightly higher than those that impart medical benefits’.

This conclusion is in line with animal data demonstrating a high sensitivity to the adverse respiratory effects of carfentanil in great apes (*Hominidae*) and underlines that extrapolating safety margins derived from rat studies (Cole & Nelson, 2017; Janssen, 1982) may be inappropriate. The actual narrow safety margin in humans may also be reflected by the extensive overlap in carfentanil blood concentrations in postmortem samples and samples from subjects whose blood was examined due to driving under influence of drugs (Sofalvi et al., 2017) (see Figure 4). However, it is unknown whether carfentanil undergoes significant postmortem redistribution, which complicates the interpretation of the blood concentration data.

Non-fatal carfentanil intoxications in drug users

The information on non-fatal intoxications associated with carfentanil use is limited in available literature. When toxicology has been performed, the levels are not always quantifiable.

Table 10 provides a summary of non-fatal intoxications and cases of driving under the influence identified in the literature involving confirmed exposure to carfentanil. The range of carfentanil concentration in blood ranged from 0.055 to 1.4 ng/mL.

The clinical features were generally consistent with opioid toxicity, and typically included reduced consciousness and respiratory depression/ arrest. While other opioids were typically detected, positive responses to naloxone were reported.

dcccxxvi) **Table 10.** Non-fatal intoxications associated with confirmed exposure to carfentanil ⁽³⁹⁾

dcccxxvii) Country	dcccxxviii) Analytical method (LOD)	dcccxxix) Cohort/case description	dcccxxx) Matrix	dcccxxxi) Reference
dcccxxxii) Bern, Switzerland	<p>dcccxxxiii) GC-MS and LC-HR-MS-MS for powder.</p> <p>dcccxxxiv) LC-MS-MS for serum and urine</p>	dcccxxxv) A 16-year-old male patient was found unconscious (Glasgow Coma Scale 3), hypotensive (71/58mmHg), tachycardic (126 bpm), hypopneic and cyanotic (peripheral oxygen saturation 70%, no signs of pulmonary edema) following the use of an unknown substance via unknown route. Body temperature was normal, pupils of normal size responding to light. After intravenous administration of naloxone and flumazenil, he regained consciousness. The urine drug screening immunoassay (Triage® TOX Drug Screen, Alere, Cologne, Germany) was negative, the blood alcohol concentration below the limit of detection. A white powder was found in the patient's belongings. And identified as carfentanil. Analysis of samples collected approximately 1 h after use with LC-MS/MS showed a serum concentration of 0.6 ng/mL for carfentanil and 0.2 ng/mL for its main metabolite norcarfentanil; urine concentrations were 1.3 ng/mL and 0.5 ng/mL, respectively.	dcccxxxvi) Powder, serum, urine	dcccxxxvii) Müller et al., 2017; Müller et al., 2017

³⁹ Carfentanil figures are in bold.

dcccxxxviii) Pennsylvania, United States	dcccxxxix) LC-MS-MS (0.03 ng/mL)	<p>dcccxli) Case 1 was a 36 year old female found unresponsive by Emergency Medical Services (EMS) in her vehicle, which was located in the middle of a highway; EMS administered 2mg of naloxone and the individual responded immediately. She was an IV heroin user and a used syringe was found on scene. Carfentanil 0.41 ng/mL; furanylfentanyl 0.17 ng/mL; delta-9 THC 0.50 ng/mL; delta-9 carboxy THC 8.5 ng/mL.</p> <p>dcccxlii) Case 2 was a 39 year old female who was located by police after 911 calls reporting erratic driving. Police found her car parked in a driveway shortly after the calls were made, conscious, but clearly under the influence of central nervous system depressants, and more specifically, narcotics. Carfentanil 0.63 ng/mL; fentanyl 3 ng/mL; norfentanyl 2.4 ng/mL.</p> <p>dcccxliii) Case 3. This human performance-related case history is not known; Male 39 years old. Carfentanil 1.3 ng/mL; furanylfentanyl 1.1 ng/mL.</p> <p>dcccxliiii) Case 3. This human performance-related case history is not known; male 36 years old. Carfentanil 1.4 ng/mL; fentanyl 4.6 ng/mL; norfentanyl 1.9 ng/mL.</p>	dcccxliv) Whole blood	dcccxlv) Papsun et al., 2017
--	----------------------------------	--	-----------------------	------------------------------

dcccxvi) United States	dcccxlvii) LC-MS-MS (0.01 ng/mL)	<p>dcccxlvi) Unconscious 28-year-old male in the driver seat of a vehicle. Took a 'bump of heroin ' and subsequently passed out. Blood sample for the driving under the influence (DUI) investigation over 2 h post arrest.</p> <p>dcccxlvi) Initial analysis: fentanyl <0.5 ng/mL; alprazolam 55 ng/mL; synthetic opioids targeted LC–MS-MS confirmed presence of carfentanil, fentanyl, furanyl fentanyl, para-fluoroisobutyl fentanyl, U-47700 and its metabolite.</p>	dcccl) blood	dcccli) Seither & Reidy, 2017
dccclii) United States	dcccliii) LC-MS-MS (0.05 ng/mL)	<p>dcccliv) 17 of 26 suspected driving under influence of drugs (DUID) cases analyzed contained carfentanil at mean and median concentrations of 0.23 and 0.19 ng/mL, respectively. A single case involving carfentanil alone was summarized.</p> <p>dccclv) Case 5. A 54-year-old male was involved in a car accident and transported by fire department ambulance to a local hospital. In the ambulance, he admitted to snorting brown heroin. He was later released from the hospital. Carfentanil 0.33 ng/mL; cotinine.</p>	dccclvi) Peripheral whole blood	dccclvii) Sofalvi et al., 2017

<p>cccclviii) United States</p>	<p>cccclix) LC-MS-MS (blood)</p> <p>cccclx)GC-MS (urine)</p>	<p>ccccxi) A 26-year-old man with a history of polysubstance abuse obtained 100mg of carfentanil via a 'dark web' source. He injected approximately 60 µg, and ingested 4.9 mg of what he believed to be 'clonazepam,' obtained from a separate online source. He was found unresponsive and bradypneic by his parents. In the emergency department, he was given a total of 4.4mg of naloxone intravenously, with partial arousal and improvement in respiratory rate. Subsequently, a naloxone infusion was initiated at 5mg/h and maintained for 7 h. The infusion was discontinued when patient had returned to baseline. Initial laboratory workup showed mild transaminase elevation and rhabdomyolysis, with peak CPK 6885 IU/L. Toxicologic studies were notable for urine immunoassay positive for opiates, benzodiazepines and cocaine. Of note, the patient also endorses using cocaine and heroin in the days prior. Benzodiazepine confirmation test was positive for alprazolam, and opiate confirmation test was positive for codeine, hydromorphone, or hydrocodone metabolite and dihydromorphone or dihydrocodeine metabolite. Urine gas chromatography/mass spectrometry (GC/MS) analysis was positive for caffeine, cocaine metabolite, and nicotine. Serum carfentanil 1.1 ng/mL.</p>	<p>cccclxii) Blood, urine</p>	<p>cccclxiii) Shulman et al., 2017</p>
---------------------------------	--	---	-------------------------------	--

<p>cccclxiv) West Virginia, United States</p>	<p>ccccclxv)</p>	<p>ccccclxvi) CHHD identified 20 opioid overdose cases within a 53-hour period in Cabell County; all cases included emergency department (ED) encounters. The most commonly reported clinical signs were altered consciousness (13; 65%) and respiratory failure (11; 55%). EMS personnel, other first responders, and ED providers administered the opioid antidote naloxone to 16 (80%) patients, six of whom were administered multiple doses. Fourteen patients (70%) reported using heroin immediately before being evaluated in the ED. Among eight (40%) patients who had toxicology screenings, opioids were detected in six. In four of these cases confirmation was sought in a public safety investigation. All four samples contained carfentanil. Other opioids confirmed in these samples were fentanyl and furanyl fentanyl. All 20 patients survived.</p>	<p>ccccclxvii) blood</p>	<p>ccccclxviii) Massey et al., 2017</p>
<p>ccccclxix) Ohio, United States</p>	<p>ccccclxx) LC-MS-MS</p>	<p>ccccclxxi) There were two cases with levels where the sample was antemortem. In these two cases, the levels were 0.055 ng/mL (also identified with acetyl fentanyl and furanyl fentanyl) and 0.370 ng/mL (also identified with alprazolam and clonazepam).</p>	<p>ccccclxxii) Peripheral blood</p>	<p>ccccclxxiii) Yin, 2017</p>

Deaths reported by the Member States

A total of 61 deaths were reported by Belgium (1), Germany (1), Estonia (6), Finland (2), Lithuania (16), Norway (1), Sweden (3) and the United Kingdom (31 cases). Carfentanil was analytically confirmed from post-mortem samples in 55 deaths and carfentanil exposure was confirmed in all deaths.

Demographics

Of the 38 deaths where demographic data were available, 32 were male (84%) and 6 were female (16%). The mean age of the males was 37 years (median 38) and ranged from 15 to 54 years. Where age was known, the females were aged 21, 28, 32, 45 years.

Number of deaths by year

Where known, the deaths occurred between November 2016 and June 2017 with all United Kingdom deaths occurring between February 2017 and June 2017.

Cause of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication). Drug paraphernalia (e.g. syringes) were reported as being present (often in situ and close by) in many cases, with some decedents still holding the equipment or a needle in the arm - suggesting that death may have occurred suddenly after administration. Whilst this is not uncommon with heroin deaths in general, it is a sign of the tolerance and toxicity threshold being reached and exceeded, likely due to the increased potency of the fentanils contributing to the opiate/opioid toxic burden.

The cause of death was reported only in 6 cases and in 5 of these intoxications with carfentanil was reported either as the primary cause of death or as likely to have contributed to death (even in presence of other substances). Where additional toxicology information was available, other substances were detected in practically all cases.

Carfentanil was quantified in 33 cases. Post-mortem blood concentrations ranged from 0.02 to 4.4 ng/mL blood (median 0.50 ng/mL blood). Due to the toxicity of potent opioids and variability in user tolerance, determination of a 'fatal' concentration based on a post-mortem blood concentration is not reliable. In the majority of circumstances involving fentanils, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use.

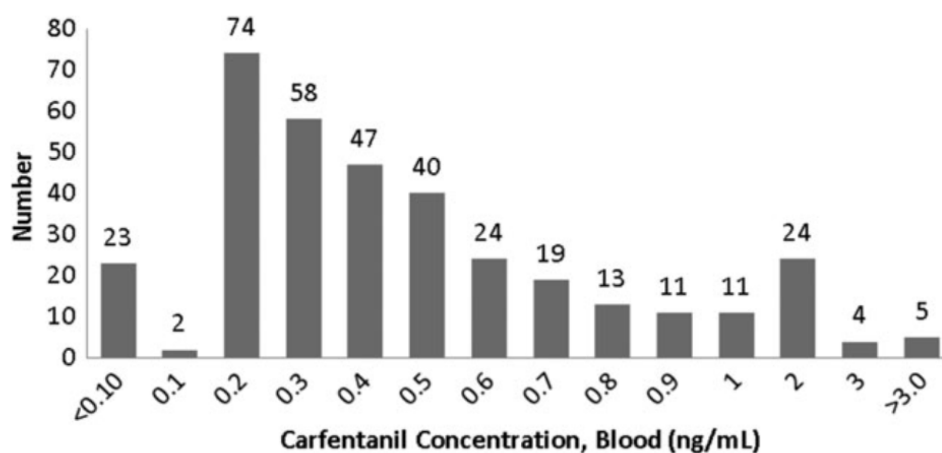
A range of other substances were detected in the deaths, including: cannabinoids, benzodiazepines, amphetamines, cocaine, antidepressants, antipsychotics, antihistamines and ethanol, etc. However, in particular, markers of heroin use (i.e. morphine, codeine, noscapine, papaverine, 6-monoacetylmorphine) as well as other opioids (including tramadol, methadone, oxycodone and dihydrocodeine) were detected in the vast majority of deaths. In terms of fentanils; fentanyl, butyrylfentanyl, 4-butyrylfentanyl, furanylfentanyl and alfentanil were detected in 23 deaths where additional toxicological information was available.

Overall, whilst other substances may have contributed some toxicity, a synergistic effect with carfentanil would have been likely with other central nervous system depressants such as ethanol, benzodiazepines, opioids (including other fentanils), etc. Nevertheless, the highly potent opioid nature of carfentanil means that the primary toxic contribution could be attributed to carfentanil and death may not have occurred if carfentanil had not been used (even where heroin was used that may not have exceeded the deceased's toxicity threshold). An assessment of the Toxicological Significance Score (TSS) (Elliott, Sedefov, and Evans-Brown, 2017) incorporating the above considerations, shows that carfentanil had a TSS value of 3 (high) in 35 out of 36 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining death, fentanyl was potentially the primary substance and carfentanil was deemed to be a secondary finding (TSS value of 2, medium). There was insufficient information available for the other cases to allow appropriate TSS assessment.

Deaths identified from other sources

Recently a large number of deaths involving carfentanil have been reported; mostly in the United States and Canada. Table 11 provides a summary of deaths identified in the literature involving confirmed exposure to carfentanil.

The distribution of blood carfentanil concentrations in 355 acute drug death cases were reported by Papsun and co-workers and is shown in Figure 3 (Papsun et al., 2017).

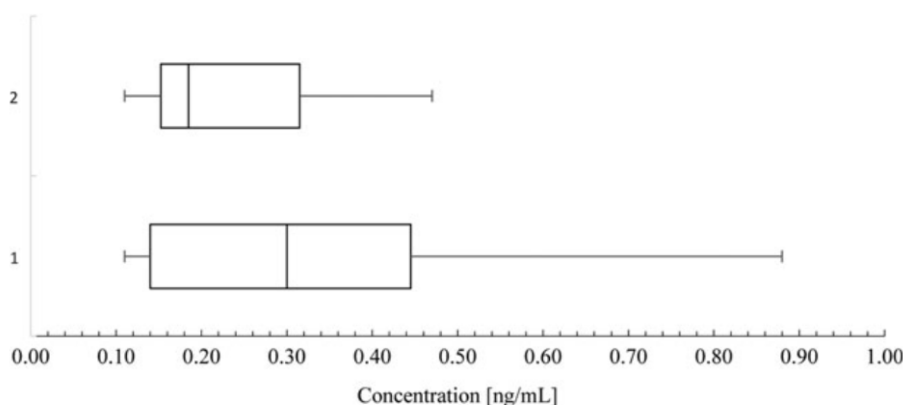


dccclxxiv)

dccclxxv) **Figure 1.** Histogram depicting positive carfentanil test results (From Papsun et al., 2017) ⁽⁴⁰⁾.

The same authors reported 4 human performance-related cases, where carfentanil concentrations (0.41, 0.63, 1.3 and 1.4 ng/mL) were more in the upper than in the lower range of the post-mortem samples (Papsun et al., 2017).

A graphic representation of blood concentrations in post-mortem cases (1; lower bar) compared to suspected driving under the influence of drugs (DUID) cases (2; upper bar) was provided by Sofalvi and co-workers as shown in Figure 4 (Sofalvi et al., 2017).



dccclxxvi)

dccclxxvii) **Figure 4.** Five-number summary for carfentanil concentrations (from Sofalvi et al., 2017) ⁽⁴¹⁾.

⁽⁴⁰⁾ Includes 4 human performance-related (non-fatal) cases.

⁽⁴¹⁾ Postmortem (1) (n = 23) and DUID (2) (n = 12) carfentanil concentration in blood: the minimum, Q1 (first quartile), the median, Q3 (third quartile) and the maximum.

In another report, carfentanil was identified in 262 post-mortem blood specimens. Blood concentrations stretched a similar range from 0.0102 to 2.0 ng/mL, with a mean concentration equal to 0.193 ng/mL and a median concentration equal to 0.0984ng/mL (Shanks & Behonick, 2017).

These data indicate that the ranges of carfentanil blood concentrations of post-mortem samples and those seen in samples from non-deceased (DUID cases) largely overlap. Similarly, overlapping ranges were shown for fentanyl and other fentanyl derivatives (Sofalvi et al., 2017).

dccclxxxix)	United States	dccxcx) MS-MS	HPLC-	<p>dccxcxi) Case 1: A 24-year-old woman with a peripheral blood carfentanil level of 0.53ng/mL. Other substances identified included delta-9 THC (0.84 ng/mL) benzoylegonine (200ng/mL), dextrorphan (200ng/mL), chlorpheniramine (240ng/mL), and dextromethorphan (2800ng/mL). Carfentanil was considered likely the primary cause of death.</p> <p>dccxcxii) Case 2: A 21-year-old man with a peripheral blood carfentanil level of 0.34 ng/mL. The remainder of his toxicology report indicated a qualitative positive result for naloxone and quantitated delta-9 THC (0.62 ng/mL), dextrorphan (91ng/mL), dextromethorphan (280 ng/mL), and chlorpheniramine (210ng/mL). Carfentanil was considered likely the primary cause of death.</p> <p>dccxcxiii) Case 3: A 20-year-old woman with a cardiac blood carfentanil level of 0.2ng/mL. Additional cardiac blood levels were furanyl fentanyl (2.5ng/mL), alprazolam (19ng/mL), cocaine (84 ng/mL), benzoylecgonine (2000 ng/mL), delta-9 THC (0.59ng/mL), and cyclobenzaprine. Carfentanil was considered likely the primary cause of death, but furanyl fentanyl and alprazolam may have contributed to death.</p>	dccxcxiv) Peripheral (case 1, 2) and cardiac (case 3) post-mortem blood	dccxcxv) Lynch et al., 2017
-------------	---------------	------------------	-------	--	---	-----------------------------

dcccxcvi)	United States	dcccxcvii) LC–MS-MS (0.03 ng/mL)	<p>dcccxcviii) 355 Samples from forensic investigations submitted between October 2016 and April 2017. Most of these cases were acute drug deaths with histories of heroin abuse where carfentanil was substituted or added to the suspected heroin obtained by the decedent. 54% of the subjects were between the ages of 25 and 40; 75% of the subjects were male.</p> <p>dcccxcix) Although not all 355 cases were tested for other drugs, when they were ~48% of positive carfentanil cases included one other opioid of which the majority were morphine and/or fentanyl; 6-acetylmorphine was confirmed in 10% of these cases. Cocaine and its metabolites was another common finding (32%).</p>	cm) Whole-blood	cmi)Papsun et al., 2017
-----------	---------------	----------------------------------	--	-----------------	-------------------------

cmii) United States	cmiii) Blood samples: LC–MS-MS (0.005 ng/mL); Urine samples (if available) were subjected to routine drugs of abuse immunoassay screening.	<p>cmiv) From 1 September 2016 to 1 January 2017, carfentanil was identified in 262 out of 657 postmortem blood specimens. Blood concentrations ranged from 0.0102 to 2.0 ng/mL, with a mean concentration equal to 0.193 ng/mL and a median concentration equal to 0.0984 ng/mL. 13 cases were summarised.</p> <p>cmv) Case 1. A 26-year-old female who had a history of drug use was seen using heroin during the night and found deceased the next morning. Autopsy findings were not available. Toxicological analysis of the iliac blood revealed carfentanil (0.234 ng/mL), 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (10.1 ng/mL) and topiramate (7.5 µg/mL). Urine was positive for buprenorphine, norbuprenorphine, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol, norfentanyl and morphine. Cause of death was certified as carfentanil intoxication. Manner of death was accident.</p> <p>cmvi) Case 2. A 38-year-old male with a history of heroin use was found unresponsive by his family in the bathroom at home. Drug paraphernalia was present at the scene. At autopsy, pulmonary congestion and cardiomegaly were observed. Toxicological analysis of the femoral blood revealed carfentanil (0.221 ng/mL). No other drugs were detected in the blood. Urine was positive for morphine, codeine, hydromorphone and norfentanyl. Cause of death was certified as carfentanil drug toxicity. Manner of death was accident.</p>	cmxix) Blood, urine	cmxx) Shanks & Behonick, 2017
---------------------	--	---	---------------------	-------------------------------

		<p>cmvii) Case 3. A 36-year-old female who had a history of drug use was found unresponsive in a bedroom of her residence. Drug paraphernalia was found in the night stand next to the bed. She was pronounced deceased at the scene. Autopsy findings included frothy pulmonary edema. Toxicological analysis of the femoral blood was positive for carfentanil (0.107ng/mL), delta-9-tetrahydrocannabinol (4.9 ng/mL) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (67.5 ng/mL). Urine was positive for temazepam, nordiazepam, oxazepam, buprenorphine, nor-buprenorphine, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol, nor-fentanyl, morphine and hydromorphone. Cause of death was certified as carfentanil drug toxicity. Manner of death was accident.</p> <p>cmviii) Case 4. A 33-year-old female was found deceased on the bathroom floor. A Narcan kit was found next to her and a dose had been used. Drug paraphernalia was found in her bedroom. The decedent had been transported to the hospital for an overdose a week prior. No other medical history was documented. Autopsy findings were not available. Toxicological analysis of the iliac blood revealed carfentanil (0.145 ng/mL), morphine (10.9 ng/mL), delta-9-tetrahydrocannabinol (2.7 ng/mL) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (29.0 ng/mL). Urine was positive for 11-nor-9-carboxy-delta-9-tetrahydrocannabinol, morphine and codeine. Cause of death was mixed drug intoxication. Manner of death was accident.</p>		
--	--	--	--	--

		<p>cmix) Case 5. A 25-year-old male who had a history of drug abuse and who had just been released from prison came home, ate a meal, and then went to bed. He was found lying in bed around 9AM and was in full rigor mortis when emergency personnel and investigators arrived a short time later. White frothy foam and purge fluid were found around the mouth and ears. A capped syringe was found in his pants pocket and vomit and other bodily fluids were found on the floor next to him. Track marks were documented on the body. Findings at autopsy included pulmonary oedema. Toxicological analysis of the heart blood revealed carfentanil (0.241 ng/mL), benzoylecgonine (54.3 ng/mL), naloxone (qualitative) and caffeine (qualitative). Urine was positive for benzoylecgonine and norfentanyl. Cause of death was certified as cocaine and carfentanil intoxication. Manner of death was accident.</p> <p>cmx) arrived a short time later. White frothy foam and purge fluid were found around the mouth and ears. A capped syringe was found in his pants pocket and vomit and other bodily fluids were found on the floor next to him. Track marks were documented on the body. Findings at autopsy included pulmonary edema. Toxicological analysis of the heart blood revealed carfentanil (0.241 ng/mL), benzoylecgonine (54.3 ng/mL), naloxone (qualitative) and caffeine (qualitative). Urine was positive for benzoylecgonine and norfentanyl. Cause of death was certified as cocaine and carfentanil intoxication. Manner of death was accident.</p>		
--	--	--	--	--

		<p>cmxi) Case 6. A 44-year-old female was found deceased. She had a history of alprazolam (Xanax®) and heroin use. No autopsy was performed. Femoral blood was positive for carfentanil (0.105 ng/mL) and cotinine (qualitative). No urine was available for testing. Cause of death was certified as carfentanil intoxication. Manner of death was accident.</p> <p>cmxii) Case 7. A 28-year-old male who had a history of heroin use was found deceased in bed in jail. Drug use the previous night had been suspected. Autopsy was negative with exception of pulmonary edema. Toxicological analysis of the iliac blood revealed carfentanil (0.0233 ng/mL) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (9.6 ng/mL). Cause of death was certified as acute carfentanil intoxication. Manner of death was accident.</p> <p>cmxiii) Case 8. A 38-year-old male, who was staying with a friend, was found lying in the bathroom deceased. A syringe, spoon and powdery substance were found on the bathroom sink. The powdery substance was identified by the local crime laboratory as a mixture of heroin, fentanyl and carfentanil. Needle marks were observed on the arms. Family stated he only had a history with drinking alcohol and no other drug history was known. No autopsy was completed. Toxicological analysis of the subclavian blood revealed carfentanil (0.0301 ng/mL). Urine was positive for morphine, hydromorphone, fentanyl and norfentanyl. Cause of death was certified as acute carfentanil toxicity. Manner of death was accident.</p>		
--	--	---	--	--

		<p>cmxiv) Case 9. A 44-year-old male was found unresponsive in bed by his girlfriend. He had a history of heroin and ethanol use. He was prescribed multiple medications including alprazolam (Xanax®), atorvastatin (Lipitor®), ondansetron (Zofran®), phenytoin (Dilantin®), quetiapine (Seroquel®) and ibuprofen (Advil®). Naloxone was administered during resuscitative attempts. Autopsy findings included needle puncture sites on both arms and the lungs were suggestive of asthmatic type bronchitis. Toxicological analysis of the femoral blood revealed carfentanil (0.114 ng/mL), furanylfentanyl (0.61 ng/mL), alprazolam (3.4 ng/mL), delta-9-tetrahydrocannabinol (2.6 ng/mL), 11-nor-9- carboxy-delta-9-tetrahydrocannabinol (3.4 ng/mL), codeine (40.0 ng/mL), buprenorphine (0.6 ng/mL), phenytoin (4.0 µg/mL), quetiapine (370 ng/mL), naloxone (qualitative), nicotine (qualitative) and cotinine (qualitative). Cause of death was certified as multiple drug (carfentanil, furanylfentanyl, codeine, buprenorphine and alprazolam) intoxication. Manner of death was accident.</p> <p>cmxv) Case 10. A 50-year-old male was found unresponsive in his truck, which was stopped and parked off the road. He was transported to the hospital and pronounced deceased. Findings at autopsy included severe pulmonary congestion and oedema, asymmetric cardiac hypertrophy, congestive splenomegaly, steatosis of the liver and left adrenal adenoma. Toxicological analysis of the subclavian blood revealed carfentanil (0.617 ng/mL) and fentanyl (2.9 ng/mL). Urine was positive for ethanol (0.2 mg/mL), fentanyl and norfentanyl. Cause of death was certified as fentanyl and carfentanil toxicity. Manner of death was accident.</p>		
--	--	---	--	--

		<p>cmxvi) Case 11. A 27-year-old male who had been living in his car was brought to the hospital by a friend. The male was unresponsive on arrival and declared deceased. Toxicological analysis of the femoral blood revealed carfentanil (0.529 ng/mL) and 11-nor-9-carboxy-delta-9- tetrahydrocannabinol (10.1 ng/mL). Urine was positive for 11-nor- 9-carboxy-delta-9- tetrahydrocannabinol, fentanyl, norfentanyl and morphine. Cause of death was certified as carfentanil toxicity. Manner of death was accident.</p> <p>cmxvii)Case 12. A 62-year-old female was found deceased in her home. She had a history of illicit and prescription drug abuse including heroin and fentanyl. She was prescribed several medications including sertraline (Zoloft®), clonidine (Catapres®), tramadol (Ultram®), gabapentin (Neurontin®) and lisinopril (Prinivil®). No autopsy was completed. Femoral blood was positive for carfentanil (0.0457 ng/mL) and fentanyl (1.1 ng/mL). No urine was available for testing. Cause of death was certified as carfentanil and fentanyl toxicity. Manner of death was accident.</p> <p>cmxviii) Case 13. A 39-year-old male, who had a history of heroin use, was found on the ground outside of his vehicle. Resuscitative attempts by emergency personnel were unsuccessful and he was pronounced deceased at the scene. The autopsy revealed no significant trauma to explain death. The lungs were congested and oedematous. Hypertensive heart disease (enlarged heart with thickened left ventricle) and hepatic steatosis were present. Needle punctures were present on the arm and hand. Toxicological analysis of the</p>		
--	--	---	--	--

		femoral blood revealed carfentanil (0.0104 ng/mL), ethanol (1.54 mg/mL), amitriptyline (29.9 ng/mL), nicotine (qualitative) and cotinine (qualitative). Urine was positive for ethanol (2.91 mg/mL). Cause of death was certified as mixed drug (carfentanil and ethanol) intoxication. Manner of death was accident.		
cmxxi) , United States	cmxxii)UHPLC-Ion Trap-MS ⁿ cmxxiii) (0.1 ng/mL)	cmxxiv) Of ≈500 postmortem samples, 375 were positive for illicit fentanyl and/or one or more fentanyl analogues. The fentanyl analogues were detected in 176 of these cases from 2015 to the end of 2016. Beginning in July 2016, carfentanil first emerged (134). Out of the 375 cases positive for illicit fentanyl and/or one or more fentanyl analogues, 70% were white males, 16% were white females, 12% were black males, and black females comprised the remaining 2%of cases. Decedents ranged in age from 17 to 73 years with a mean of 38 years and a median of 36 years. Summaries of 12 cases were provided. Below only those involving carfentanil (7) are listed. cmxxv) Case 5. 34 year old white female found slumped over in front seat of minivan. Mother of four minor children, history of illicit drug use. Carfentanil; furanyl fentanyl; despropionyl fentanyl; cocaine 11 ng/mL; benzoylecgonine 124 ng/mL; methylecgonidine; methylecgonine; levamisole; cannabinoids. Cause and manner of death: Acute combined drug toxicity (carfentanil, furanyl fentanyl and cocaine) - accident.	cmxxxii) Blood, urine, tissue	cmxxxiii) Shoff et al., 2017

		<p>cmxxvi) Case 6. 37 year old white male found behind bushes decomposed. Carfentanil; ethanol 0.089% (bile), 0.051% (brain); dextromethorphan; diphenhydramine; hydroxyzine; ibuprofen; meprobamate; quetiapine; sertraline; nortriptyline; cannabinoids. Cause and manner of death: Carfentanil toxicity - accident.</p> <p>cmxxvii) Case 7. 27 year old white female. Prostitute found unresponsive in a field with drug paraphernalia littering the area. Carfentanil; fentanyl 12 ng/mL; morphine 13 ng/mL; codeine <0.01 µg/mL; 6-monoacetylmorphine <1 ng/mL; cocaine <10 ng/mL; benzoylecgonine 125 ng/mL; methylecgonine; chlorcyclizine; hydroxyzine. Cause and manner of death: Acute combined drug toxicity (cocaine, heroin, carfentanil, fentanyl) – accident.</p> <p>cmxxviii) Case 8. 23 year old white male found unresponsive in bathroom by his family with drug paraphernalia. Carfentanil; parafluoroisobutyryl fentanyl; ethanol 0.084% (blood), 0.107% (ocular); dextromethorphan. Cause and manner of death: Acute combined drug toxicity (carfentanil, para-fluorobutyryl/para-fluoroisobutyryl fentanyl and ethanol) – accident.</p>		
--	--	--	--	--

		<p>cmxxix) Case 9. 19 year old white male. Suspected supplier of fentanyl on house arrest Transported to hospital unresponsive and died 6 days later. Carfentanil; furanyl fentanyl; Despropionyl fentanyl; morphine <10 ng/mL; codeine <10 ng/mL; cocaine <10 ng/mL; benzoylecgonine 209 ng/mL; methylecgonidine; methylecgonine; levamisole; 7-aminoclonazepam; ibuprofen; lidocaine; desethylidocaine; naloxone; cannabinoids. Cause and manner of death: Acute cocaine and synthetic opiate toxicity – accident.</p> <p>cmxxx) Case 10. 41 year old white male found unresponsive in a field. Carfentanil; U-47700; fentanyl <1 ng/mL; morphine 32 ng/mL; codeine <10 ng/mL; cocaine <0.01 mg/L; methylecgonine; atropine; diphenhydramine; gabapentin; ibuprofen; naloxone; quetiapine; norquetiapine; quinine. Cause and manner of death: Acute combined drug toxicity (carfentanil, fentanyl, probable heroin, U-47700, diphenhydramine and cocaine) – accident.</p> <p>cmxxxi) Case 12. 30 year old white male found unresponsive on the street with a foamy discharge around his mouth. Carfentanil; parafluoroisobutyryl fentanyl; U-47700; sertraline; nortriptyline; diphenhydramine. Cause and manner of death: Acute bronchopneumonia acute combined drug toxicity (carfentanil, para-fluoroisobutyryl fentanyl, diphenhydramine and U-47700) – accident.</p>		
--	--	--	--	--

cmxxxiv) , United States	cmxxxv) LC-MS-MS (0.05 ng/mL)	<p>cmxxxvi) 31 of 98 postmortem cases contained carfentanil at mean and median concentrations of 0.34 and 0.30 ng/mL, respectively. A single case involving carfentanil was summarized.</p> <p>cmxxxvii) Case 4. A 31-year-old female presented to a local hospital from home via EMS and died 10 min after arrival. She had a history of heroin and prescription pill abuse, seizures and asthma. At autopsy, she was found with numerous recent and healing puncture wounds of ankles, hands and wrists. She had bilateral pulmonary edema with the increased lung weights of 670 and 540 g for the right and left lungs, respectively. Carfentanil 1.9 ng/mL (heart blood), 0.36 ng/mL (femoral blood); <1 ng/mL fentanyl; 88 ng/mL morphine; <10 ng/mL codeine; <4 ng/mL 6-AM; 19 ng/mL clonazepam; 22 ng/mL oxazepam; 110 ng/mL temazepam; 100 ng/mL cyclobenzaprine in femoral blood. The femoral blood was also positive for diphenhydramine, nicotine, meprobamate and 7-aminoclonazepam. The cause of death was ruled as acute intoxication by the combined effects of carfentanil, heroin, benzodiazepines and cyclobenzaprine.</p>	cmxxxviii) Blood, vitreous humour	cmxxxix) Sofalvi et al., 2017
--------------------------	-------------------------------	---	-----------------------------------	-------------------------------

cmxl) Florida, United States	cmxli)	<p>cmxlii) Case 1. A 34-year-old white male was found dead in a van located in a car wash. The deceased was slumped over in the driver's seat of the van with the car running. 9-1-1 was called, paramedics responded and he was pronounced dead at the scene. A syringe, spoon and a yellow baggy with a brown coloured substance was located in the cup holder in the centre console. He had a history of tobacco, alcohol, marijuana and heroin abuse. Autopsy findings were unremarkable except for mild hypertensive heart disease with left ventricular hypertrophy and mild hepatic steatosis. No other disease was noted. Carfentanil 1.3 ng/mL (heart blood); furanyl fentanyl 0.34 ng/mL (heart blood); fentanyl 6 ng/mL (heart blood); morphine <20 ng/mL (heart blood), present (urine); hydromorphone <20 ng/mL (heart blood), present (vitreous humour, urine); 6-MAM present (vitreous humour, urine); hydrocodone present (vitreous humour, urine). Cause and manner of death: Intoxication by the combined effects of heroin, fentanyl, carfentanil and furanyl fentanyl - accident.</p> <p>cmxliii) Case 2. A 25-year-old white male was having financial and relationship problems and was living in a tent with his mother at a county park. He last spoke with his sister by phone and sounded 'very intoxicated '. His mother noted he was 'itching all over ', left for work, and when she returned home her son was lying prone on a mattress in the tent. 9-1-1 was called, paramedics responded and he was pronounced dead at the scene. A baggy with a brown substance was found next to the deceased. He had a history of tobacco, alcohol, marijuana, spice and prescription pain medication abuse. Autopsy findings were unremarkable except for mild left ventricular hypertrophy. No other disease was noted.</p>	cmxliv) Peripheral and heart blood, vitreous humour	cmxlv) Swanson et al., 2017
------------------------------	--------	--	---	-----------------------------

		Carfentanil 0.12 ng/mL (heart blood); benzoylecgonine 460 ng/mL (peripheral blood), 510 ng/mL (vitreous humour); cocaine 40 ng/mL (vitreous humour). Cause and manner of death: Intoxication by carfentanil - accident.		
cmxlvii)United States	cmxlviii)	<p>cmxlviii) Case 1: A 31-year old male with reported history of heroin abuse found deceased near drug paraphernalia. Blood testing revealed evidence of both carfentanil and ethanol. Carfentanil 0.13 ng/mL; ethanol 0.226 g/dL. Cause of death was attributed to mixed carfentanil and ethanol toxicity.</p> <p>cmxlix)Case 2: A 33-year old male with reported history of substance abuse, including heroin and fentanyl, found deceased near drug paraphernalia. Blood testing revealed evidence of carfentanil and ethanol. Carfentanil 0.64 ng/mL; ethanol 0.177 g/dL. Cause of death was attributed to acute carfentanil and ethanol toxicity.</p> <p>cml)Case 3: A 42-year-old female with history of recent overdose reversed with naloxone found deceased near drug paraphernalia. Carfentanil 0.27 ng/mL; methamphetamine 20 ng/mL; morphine 30 ng/mL; alprazolam 15 ng/mL; ethanol 0.02 g/dL. Cause of death was attributed to mixed drug toxicity.</p> <p>cml) Case 4: A 34-year-old female with history of substance abuse including heroin found deceased near drug paraphernalia. Carfentanil 0.44 ng/mL; methamphetamine 180 ng/mL; benzoylecgonine 150 ng/mL; morphine 60 ng/mL; clonazepam 2.7 ng/mL; 7-amino-clonazepam 160 ng/mL. Cause of death was attributed to mixed drug toxicity.</p>	<p>cmliii) Blood, urine</p> <p>cmliv)</p>	cmlv) Olives et al., 2017

		<p>cmlii) Case 5: A 23-year-old male with history of heroin abuse found deceased near drug paraphernalia. Carfentanil 0.14 ng/mL; ethanol 0.023 g/dL; urine 6-monoacetyl morphine 6 ng/mL. Cause of death was attributed to acute carfentanil toxicity</p>		
cmlvi) Ohio, United States	cmlvii) LC-MS-MS ⁴³	<p>cmlviii) There were a total of 49 deaths. The mean age was 42 (range 21–63). Gender breakdown was males 35 (71.4%), female 14 (28.6%). Race makeup was white 43 (88%), black 4 (8%), and Hispanic 2 (2%). Deaths peaked in the month of September with 22. 32 of the 49 cases had known quantitative carfentanil levels which ranged from 0.013 to 1.3 ng/mL. The mean carfentanil level was 0.259 ng/mL. Fentanyl, fentanyl analogues, or morphine/6-monoacetylmorphine (6-MAM) were found in 33 of the cases. Eleven cases with quantitative levels did not have another opioid identified. The mean carfentanil level for those 11 cases was 0.350 ng/mL. The most common other agents were fentanyl (15), morphine/6-MAM (30), ethanol (14), and cocaine (11). Acetyl fentanyl and furanyl fentanyl were the only other fentanyl analogues identified.</p>	cmlix) Peripheral blood	cmlx) Yin, 2017

⁽⁴³⁾ Part of the samples have been analysed by NMS labs, Willow Grove, PA. Therefore, some of these cases are likely included in those reported by Papsun et al., (2017).

D2. Chronic health effects

D2.1. Animal data

There are no studies identified on the long-term effects of carfentanil in animals. Due to its high potency, the pharmacological dose of carfentanil is very low. This makes it less likely that unexpected toxicity would occur, even after repeated exposure. The adverse effects to be anticipated are those related to the pharmacological action of carfentanil.

Fentanyl toxicity has been summarized in the European Assessment Report for Effentora®, a fentanyl-containing buccal tablet (EMA, 2008). In rats, deaths occurred following oral doses of 10 mg/kg/day or more and following IM doses of 0.1 to 0.4 mg/kg/day. The main findings in these studies were weight loss or reductions in weight gain. There was no clear-cut evidence of target organ toxicity, although the data are limited, and the cause of death was considered to be associated with respiratory depression.

In rabbits, fentanyl was well-tolerated when administered by the transcutaneous route for up to 90 days at a dose of 0.66 mg/kg/day (EMA, 2008).

In dogs, IM administration of fentanyl at doses of 0.1 and 0.4 mg/kg/day for 30 days produced weight loss and/or no weight gain over the 30 day test period. Intravenous administration of 0.1, 0.3 and 1.0 mg/kg fentanyl to dogs for 30 days again produced a decrease in body weight at the highest dose, with dose-related clinical signs of sedation and convulsions. All dogs survived both the 30 day IM and IV dosing periods (EMA, 2008).

Fentanyl is not considered to be genotoxic; carcinogenicity studies have not been performed (EMA, 2008).

Studies with fentanyl in female rats revealed reduced fertility and enhanced embryonal mortality. More recent studies showed that effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed. Teratogenic effects have not been demonstrated (EMA, 2008).

D2.2. Human data

No studies were identified that have examined the chronic health effects of carfentanil.

Fentanyl is used clinically for pain treatment. Rodríguez reviewed the use of different oral or nasal transmucosal fentanyl formulations. The proportion of fentanyl-treated patients presenting an adverse effect (AE) was high (about two out of three subjects receiving fentanyl). As expected, the most frequently reported AEs were those associated with opioid use (nausea, vomiting, dizziness, constipation, and drowsiness). The impact of those effects was, in general, mild and not leading to treatment discontinuation during treatment phase or even at long term. However, it is suspected that the safety may be overestimated, since most studies have been done in the short term and the methods have been focused mainly on assessing effectiveness (Rodríguez et al., 2015).

D3. Factors affecting public health risks

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

Carfentanil is being sold by vendors on the surface web and dark web as a drug in its own right. It is sold in both wholesale and consumer quantities. In addition, carfentanil is being mixed with or sold as heroin and other opioids on the illicit opioid market in at least three countries in Europe.

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

Due to its relatively recent availability on the drug market, the availability of information, degree of knowledge and perceptions amongst users concerning carfentanil and its effects are limited. In addition, given that carfentanil has been mixed with or sold as heroin and other illicit opioids, many users will be unaware that they are using the drug.

D3.3. Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviours of users of carfentanil. The available information on characteristics and behaviour of users is provided in Section D3.4.

D3.4. Nature and extent of health consequences

Acute health risks

The available data suggests that the nature of the acute effects of carfentanil share some similarities with opioid analgesics such as morphine and fentanyl.

The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, and respiratory depression. They also have an abuse liability and dependence potential (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; Romberg et al., 2003).

Similar to other opioid analgesics, the most serious acute risk arising from the use of carfentanil is likely to be from rapid and profound respiratory depression, which can lead to apnoea, respiratory arrest, and death (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; White & Irvine, 1999).

For fentanils in general, this risk may be exacerbated by:

- the difficulty in diluting/using fentanils (as they are typically highly potent), which can lead to a toxic dose being accidentally used (de Boer et al., 2003; Sutter et al., 2017);
- the apparent rapid onset of severe poisoning following use (Somerville et al., 2017);
- using routes of administration that allow large amounts of the substance to rapidly reach the central nervous system (such as injecting, insufflation, and inhalation) (e.g. Macleod et al., 2012);
- availability of easy to use dosage forms (such as nasal sprays and e-liquids) (e.g. Macleod et al., 2012);
- lack of awareness and experience of users with these new substances (effects and dosage);
- use of other central nervous system depressants (such as other opioids, benzodiazepines, and alcohol) (e.g. van der Schrier et al., 2017)
- lack of tolerance to opioids in opioid-naïve persons (such as new or former users);
- use in environments where it may be difficult to summon help in the event of poisoning (e.g. alone in a home environment) (Somerville et al., 2017);
- limited availability of the antidote naloxone in community settings (EMCDDA, 2015; EMCDDA, 2016; Somerville et al., 2017).

In addition, and, often unknown to users, the fentanils are mixed with or sold as heroin and other illicit opioids. They are also used to make counterfeits of highly sought-after medicines, such as opioid analgesics and benzodiazepines. They have also been sold in or as drugs such as cocaine (Klar et al., 2016; SFDPH, 2015; Sutter et al., 2017; Tomassoni et al., 2017). Due to this, users may not be aware that they are using a fentanyl; in some cases these individuals will have no tolerance to opioids nor access to community naloxone programmes. Overall, these factors may increase the risk of life-threatening poisoning.

Given the above risks, poisonings by fentanils may manifest as outbreaks which have the potential to overwhelm emergency responders and other local healthcare systems (Klar et al., 2016; SFDPH, 2015; Sutter et al., 2017; Tomassoni et al., 2017).

Accidental exposure to the fentanils may also pose a risk to non-users, including family and friends, law enforcement and emergency responders. Such risks may need to be assessed so that, where required, appropriate procedures, training and environmental and personal protective measures can be provided for handling materials suspected to contain these substances (IAB, 2017; Moss et al., 2017; US CDC, 2016; US DEA, 2017). Any responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole & Nelson, 2017; Lynch, Suyama, & Guyette, 2017).

Managing poisoning

The antidote naloxone will reverse acute poisoning caused by carfentanil (Kim and Nelson, 2015; Ujváry et al., 2017).

Carfentanil has been characterized as a quick-acting analgesic with a short duration of action (Jacobson, 1988; Janssen, 1982). Yet, renarcotisation has been observed in animals when these have not been reversed with a sufficiently high dose of a μ -opioid antagonist, or when an antagonist with a short duration of action is used (Miller et al., 1996; Portas, 2004). Redistribution from (fatty) tissues of carfentanil—due to its lipophilic nature—could be a possible factor contributing to this effect.

Recent clinical and community experience in treating poisonings caused by carfentanil suggests that larger than normal doses and repeated doses of naloxone may be required to manage the poisoning in some cases; longer periods of observation may also be required (US CDC, 2013; Klar et al., 2016; Moss et al., 2017; Somerville et al., 2017; Sutter et al., 2017). This may reflect, among other factors, the high potency of the fentanils, their half-lives, the dose an individual is exposed to, and the relatively short half-life of naloxone. This may necessitate different strategies in treating opioid overdose patients, where fentanils, including carfentanil, could be involved. This may include repeated or higher doses of antagonists and longer periods of observation (Cole & Nelson, 2017; Lust et al., 2011).

Chronic health risks

While there is limited data, the chronic health risks of carfentanil might share some similarities to opioids such as heroin and other fentanils. This may include dependence.

D3.5. Long-term consequences of use

While there is limited data, the chronic health risks of carfentanil might share some similarities to opioids such as heroin and other fentanils. This may include dependence.

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

There is limited data on the conditions which carfentanil is obtained and used in Europe. Carfentanil has been sold on the surface web and darknet marketplaces, typically as powders. In addition, it has also been mixed with or sold as heroin and other opioids on the illicit opioid market.

Section E. Social Risks

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

E1. Individual social risks

There is no information on the individual social risks that may be associated with the use of carfentanil. Given that carfentanil acts as an opioid analgesic, any such risks may have some similarities with those associated with illicit opioids. These may negatively impact on education or career, family or other personal and social relationships and may result in marginalisation.

E2. Possible effects on direct social environment

There is no information on the possible effects of carfentanil on the direct social environment. Given that carfentanil appears to act as an opioid analgesic, any such effects may have some similarities with those associated with the use of illicit opioids.

E3. Possible effects on society as a whole

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

As discussed above, accidental exposure to the fentanils may pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel as well as custodial settings and postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in managing poisoning (including in resuscitation and administration of naloxone to reverse poisoning). Any required responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole & Nelson, 2017; Lynch, Suyama, & Guyette, 2017).

E4. Economic costs

There are no data on the health and social costs related to carfentanil.

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

There are no data on the possible effects of carfentanil related to the cultural context.

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

While no specific examples are available on the possible appeal of carfentanil to specific user groups (aside from psychonauts), it is reasonable to assume carfentanil may be sought by those looking for 'legal' substitutes for illicit opioids, such as heroin and/or prescription opioids.

Section F. Involvement of organised crime

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

There is limited information on the involvement of organised crime or established criminal groups in the manufacture, distribution and supply of carfentanil.

In this respect, Estonia reported that almost all trafficking and distribution of fentanils, including carfentanil, is linked with organised crime groups in Estonia. In addition, they reported that these groups are keeping dealers under control through violence.

The United Kingdom reported to Europol 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 ⁽⁴⁴⁾.

In addition, the United Kingdom's National Crime Agency (NCA) reported to Europol 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 milligrams (15 orders) to 1 gram (1 order).

In the cases reported to Europol where the country of origin for the seizures was known, the countries were: China (specifically Hong Kong), the United Kingdom and Germany were also mentioned, but to a lesser extent ⁽⁴⁵⁾.

Germany reported a seizure of carfentanil by Canadian law enforcement in Vancouver, in June 2017. The carfentanil was detected in a package which was en-route from Hong Kong to Canada via Germany, using Deutsche Post DHL.

⁽⁴⁴⁾ Canada reported that there is no evidence to date to indicate carfentanil production in the country. They also reported that they have not really seen any traditional organised crime group involvement or that the involvement is limited and that the darknet is often used to conduct transactions.

⁽⁴⁵⁾ Carfentanil is sold as counterfeit oxycodone (CDN 80) or Xanax tablets and is also imported in powder form and then tableted in the country. Canada reported 6 carfentanil seizures in 2016 which occurred at the Vancouver and Montreal international mail centres. The country of origin was reported as China (5 seizures) and Hong Kong (1). In 2017, 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).

Lithuania reported that there are indications that carfentanil may be imported from Russia and China. They also reported that carfentanil is often mixed with heroin and prepared for heroin users and most cases are related to heroin distribution in the local Roma community.

Sweden indicated that carfentanil has been bought from internet vendors and delivered directly to the user from China, the United Kingdom and Germany. They reported that there are no indications of the domestic sale of carfentanil in Sweden.

The United Kingdom reported that it was unclear how much, if any, carfentanil has been manufactured in the United Kingdom. Information indicates that it has been shipped from China/Hong Kong and the substance has been used as received, or mixed with other drugs, for example heroin, or cutting agents before being used or sold on.

Latvia reported 6 seizures of carfentanil to the EMCDDA which occurred inside a prison or custodial setting.

The seizure of an illicit laboratory in Europe in 2013 that was producing fentanils demonstrates the capability to manufacture fentanils exists within the European Union.

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

No information was reported or identified concerning the impact of carfentanil on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances.

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

No information was reported nor identified concerning evidence of the same groups of people being involved in different types of crime related to the availability of carfentanil.

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

No information was reported nor identified concerning incidents of violence related to the availability of carfentanil.

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

No information was reported nor identified concerning evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society related to the availability of carfentanil.

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

No information was reported nor identified concerning the economic costs and consequences related to the availability of carfentanil.

F7. Use of violence between or within criminal groups

No information was reported nor identified concerning the use of violence between or within criminal groups related to the availability of carfentanil.

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

No information was reported nor identified concerning evidence of strategies to prevent prosecution related to the availability of carfentanil.

References

Aceto, M., Bowman, E., Harris, L., & May, E. (1988), 'Dependence studies of new compounds in the rhesus monkey, rat and mouse (1988)', *National Institute on Drug Abuse Research Monograph*, 90, pp. 468–515.
<https://archives.drugabuse.gov/pdf/monographs/90.pdf>

Bagley, J. R., Thomas, S. A., Rudo, F. G., Spencer, H. K., Doorley, B. M., Ossipov, M. H., Spaulding, T. (1991), 'New 1-(heterocyclalkyl)-4-(propionanilido)-4-piperidinyl methyl ester and methylene methyl ether analgesics', *Journal of Medicinal Chemistry*, 34(2), pp. 827–841.

Baker, J. R., & Gatesman, T. J. (1985), 'Use of carfentanil and a ketamine-xylazine mixture to immobilise wild grey seals (*Halichoerus grypus*)', *The Veterinary Record*, 116(8), pp. 208–210.

Barratt, D. T., Bandak, B., Klepstad, P., Dale, O., Kaasa, S., Christrup, L. L., Somogyi, A. A. (2014), 'Genetic, pathological and physiological determinants of transdermal fentanyl pharmacokinetics in 620 cancer patients of the EPOS study', *Pharmacogenetics and Genomics*, 24(4), pp. 185–194.
<https://doi.org/10.1097/FPC.0000000000000032>

Baylon, G. J., Kaplan, H. L., Somer, G., Busto, U. E., & Sellers, E. M. (2000), 'Comparative abuse liability of intravenously administered remifentanyl and fentanyl', *Journal of Clinical Psychopharmacology*, 20(6), pp. 597–606.
<http://www.ncbi.nlm.nih.gov/pubmed/11106130>

Blecha, J. E., Henderson, B. D., Hockley, B. G., VanBrocklin, H. F., Zubieta, J.-K., DaSilva, A. F., Shao, X. (2017), 'An updated synthesis of [11C]carfentanil for positron emission tomography (PET) imaging of the μ -opioid receptor', *Journal of Labelled Compounds & Radiopharmaceuticals*, 60(8), pp. 375–380.
<https://doi.org/10.1002/jlcr.3513>

Casale, J. F., Mallette, J. R., & Guest, E. M. (2017), 'Analysis of illicit carfentanil: Emergence of the death dragon', *Forensic Chemistry*, 3, pp. 74–80. <https://doi.org/10.1016/j.forc.2017.02.003>

Caulkett, N. A., Cribb, P. H., & Haigh, J. C. (2000), 'Comparative cardiopulmonary effects of carfentanil-xylazine and medetomidine-ketamine used for immobilization of mule deer and mule deer/white-tailed deer hybrids', *Canadian Journal of Veterinary Research*, 64(1), pp. 64–68.

Cayman Chemical Company (2016). Carfentanil safety data sheet. Ann Arbor, MI, USA. <https://www.caymanchem.com/msdss/19410m.pdf>

Cerilliant. (n.d.), 'Carfentanil Oxalate'. Retrieved September 11, 2017. Available from https://www.cerilliant.com/shoponline/Item_Details.aspx?itemno=c0ec9694-2e7e-4eec-9b4b-aa2f836c7ee6&item=C-162-1EA

Cheney, C. S., & Hattingh, J. (1988), 'Effects of chemical immobilisation on the blood composition of impala (*Aepyceros melampus* (Lichtenstein))', *Journal of the South African Veterinary Association*, 59(1), pp. 13–18.

Cole, A., Mutlow, A., Isaza, R., Carpenter, J. W., Koch, D. E., Hunter, R. P., & Dresser, B. L. (2006), 'Pharmacokinetics and pharmacodynamics of carfentanil and naltrexone in female common eland (*Taurotragus oryx*)' *Journal of Zoo and Wildlife Medicine*, 37(3), pp. 318–326. <https://doi.org/10.1638/05-070.1>

Cole, J. B., & Nelson, L. S. (2017), 'Controversies and carfentanil: We have much to learn about the present state of opioid poisoning'. *The American Journal of Emergency Medicine*. <https://doi.org/10.1016/j.ajem.2017.08.045>

Colpaert, F. C., Kuyps, J. J., Niemegeers, C. J., Janssen, P. A. (1976), 'Discriminative stimulus properties of fentanyl and morphine: tolerance and dependence', *Pharmacology, biochemistry, and behaviour*, 5(4), pp. 401–408.

Costa, E. M., Hoffmann, B. B., & Loew, G. H. (1992), 'Opioid agonists binding and responses in SH-SY5Y cells', *Life Sciences*, 50(1), pp. 73–81.

Cox, B. M. (2011), Pharmacology of opioid drugs, in: *G. Pasternak (ed) The opiate receptors*. Springer, pp. 23–58.

Cushing, A., McClean, M., Stanford, M., Lohe, T., Alcantar, B. E., & Chirife, A. D. (2011), Anesthesia of Tibetan yak (*Bos grunniens*) using thiafentanil - xylazine and carfentanil – xylazine, *Journal of Zoo and Wildlife Medicine*, 42(4), pp. 713–717. <https://doi.org/10.1638/2010-0140.1>

Dahan, A., Sarton, E., Teppema, L., Olievier, C., Nieuwenhuijs, D., Matthes, H. W. and Kieffer B. L. (2001), 'Anesthetic potency and influence of morphine and sevoflurane on respiration in mu-opioid receptor knockout mice', *Anesthesiology*, 2001, 94(5), pp. 824–832.
<http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1944782>

Daniulaityte, R., Juhascik, M. P., Strayer, K. E., Sizemore, I. E., Harshbarger, K. E., Antonides, H. M., & Carlson, R. R. (2017), 'Overdose deaths related to fentanyl and its analogs - Ohio, January-February 2017', *MMWR. Morbidity and Mortality Weekly Report*, 66(34), pp. 904–908.
<https://doi.org/10.15585/mmwr.mm6634a3>

Dannals, R. F., Ravert, H. T., Frost, J. J., Wilson, A. A., Burns, H. D., & Wagner, H. N. J. (1985), 'Radiosynthesis of an opiate receptor binding radiotracer: [¹¹C]carfentanil', *The International Journal of Applied Radiation and Isotopes*, 36(4), pp. 303–306.

de Boer, D., Goemans W. P., Ghezavat, V. R., van Ooijen, R. D., Maes, R. A. (2003), 'Seizure of illicitly produced para-fluorofentanyl: quantitative analysis of the content of capsules and tablets', *Journal of Pharmaceutical and Biomedical Analysis*, 31(3), pp. 557–562.

de Castro, J., Van de Water, A., Wouters, L., Xhonneux, R., Reneman, R., & Kay, B. (1979a), 'Comparative study of cardiovascular, neurological and metabolic side effects of eight narcotics in dogs. Pethidine, piritramide, morphine, phenoperidine, fentanyl, R 39 209, sufentanil, R 34 995. I. Comparative study on the acute toxicity and hemodynamic effects of the narcotics in high and massive doses in curarised and mechanically ventilated dogs', *Acta Anaesthesiologica Belgica*, 30(1), pp. 5–54.
<http://www.ncbi.nlm.nih.gov/pubmed/382728>

de Castro, J., Van de Water, A., Wouters, L., Xhonneux, R., Reneman, R., & Kay, B. (1979b), 'Comparative study of cardiovascular, neurological and metabolic side effects of eight narcotics in dogs. Pethidine, piritramide, morphine, phenoperidine, fentanyl, R 39 209, sufentanil, R 34 995. II. Comparative study on the epileptoid activity of the narcotics used in high and massive doses in curarised and mechanically ventilated dogs' *Acta Anaesthesiologica Belgica*, 30(1), pp. 55–69. <http://www.ncbi.nlm.nih.gov/pubmed/474064>

de Castro, J., Van de Water, A., Wouters, L., Xhonneux, R., Reneman, R., & Kay, B. (1979c), 'Comparative study of cardiovascular, neurological and metabolic side effects of eight narcotics in dogs. Pethidine, piritramide, morphine, phenoperidine, fentanyl, R 39 209, sufentanil, R 34 995. III. Comparative study of the acute metabolic toxicity of the narcotics used in high and massive doses in curarised and mechanically ventilated dogs' *Acta Anaesthesiologica Belgica*, 30(1), pp. 71–90.
<http://www.ncbi.nlm.nih.gov/pubmed/38620>

De Vos, V. (1978), 'Immobilisation of free-ranging wild animals using a new drug', *Veterinary Record*, 103(4), pp. 64–68. <http://dx.doi.org/10.1136/vr.103.4.64>

Delvaux, H., Courtois, R., Breton, L., & Patenaude, R. (1999), 'Relative efficiency of succinylcholine, xylazine, and carfentanil/xylazine mixtures to immobilize free-ranging moose', *Journal of Wildlife Diseases*, 35(1), pp. 38–48. <https://doi.org/10.7589/0090-3558-35.1.38>

Elliott, S., Sedefov, R. and Evans-Brown, M. (2017), 'Assessing the toxicological significance of new psychoactive substances in fatalities', *Drug Testing and Analysis*. <https://doi.org/10.1002/dta.2225>

European Medicines Agency (EMA) (2008). Effentora EPAR. London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000833/WC500020928.pdf

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2015). Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone. EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/system/files/publications/932/TDAU14009ENN.web_.pdf

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2016). Preventing opioid overdose deaths with take-home naloxone. Luxembourg, Publications Office of the European Union, 2016. <https://doi.org/10.2810/357062>

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2017a). EMCDDA–Europol Joint Report on a new psychoactive substance: methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil), Luxembourg, Publications Office of the European Union.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2017b). Report on the risk assessment of *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacrylamide (acryloylfentanyl) in the framework of the Council Decision on new psychoactive substances, Luxembourg, Publications Office of the European Union.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2017b). Report on the risk assessment of *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide (furanlylfentanyl) in the framework of the Council Decision on new psychoactive substances, Luxembourg, Publications Office of the European Union.

Endres, C. J., Bencherif, B., Hilton, J., Madar, I., & Frost, J. J. (2003), 'Quantification of brain μ -opioid receptors with [^{11}C]carfentanil: reference-tissue methods', *Nuclear Medicine and Biology*, 30(2), pp. 177–186.

Erhardt, W., Hebestedt, A., Aschenbrenner, G., Pichotka, B., & Blümel, G. (1984), 'A comparative study with various anesthetics in mice (pentobarbitone, ketamine-xylazine, carfentanyl-etomidate)' *Research in Experimental Medicine*. Zeitschrift Fur Die Gesamte Experimentelle Medizin Einschliesslich Experimenteller Chirurgie, 184(3), pp. 159–169.

Eriksson, O., & Antoni, G. (2015), '[^{11}C]Carfentanil binds preferentially to mu-opioid receptor subtype 1 compared to subtype 2', *Molecular Imaging*, 14, pp. 476–483.

Feasel, M. G., Wohlfarth, A., Nilles, J. M., Pang, S., Kristovich, R. L., & Huestis, M. A. (2016), 'Metabolism of carfentanil, an ultra-potent opioid, in human liver microsomes and human hepatocytes by high-resolution mass spectrometry' *The AAPS Journal*, 18(6), pp. 1489–1499. <https://doi.org/10.1208/s12248-016-9963-5>

Feldman, P. L. & Brackeen, M. F. (1990), 'A novel route to the 4-anilido-4-(methoxycarbonyl)piperidine class of analgetics' *Journal of Organic Chemistry*, 55(13), pp. 4207–4209.

Fitzgerald, L. W., & Teitler, M. (1993), 'Quantitative autoradiographic analysis of [³H]carfentanil binding to mu opiate receptors in the rat brain' *Synapse* (New York, N.Y.), 14(2), pp. 154–159.
<https://doi.org/10.1002/syn.890140208>

Frost, J. J., Wagner, H. N. Jr., Dannals, R. F., Ravert, H. T., Links, J. M., Wilson, A. A., Synder, S. H.. (1985), 'Imaging opiate receptors in the human brain by positron tomography', *Journal of Computer Assisted Tomography*, 9(2), pp. 231–236. <https://doi.org/10.1126/science.6604315>

Frost, J. J., Douglass, K. H., Mayberg, H. S., Dannals, R. F., Links, J. M., Wilson, A. A., et al. (1989), 'Multicompartmental analysis of [¹¹C]-carfentanil binding to opiate receptors in humans measured by positron emission tomography' *Journal of Cerebral Blood Flow and Metabolism*, 9(3), pp. 398–409.

George, A. V, Lu, J. J., Pisano, M. V, Metz, J., & Erickson, T. B. (2010), 'Carfentanil—an ultra potent opioid' *The American Journal of Emergency Medicine*, 28(4), pp. 530–532.
<https://doi.org/10.1016/j.ajem.2010.03.003>

Gerrits, M. A. F. M., Lesscher, H. B. M., & van Ree, J. M. (2003), 'Drug dependence and the endogenous opioid system', *European Neuropsychopharmacology*, 13(6), pp. 424–434. <https://doi.org/10.1016/j.euroneuro.2003.08.003>

Guillon, J., Buronfosse, T., Désage, M., Lepape, A., Brazier, J.-L., & Beaune, P. (1997), 'Possible involvement of multiple cytochrome P450S in fentanyl and sufentanil metabolism as opposed to alfentanil', *Biochemical Pharmacology*, 53(11), pp. 1613–1619. [https://doi.org/10.1016/S0006-2952\(96\)00893-3](https://doi.org/10.1016/S0006-2952(96)00893-3)

Haigh, J. C., & Gates, C. C. (1995), *Capture of wood bison (Bison bison athabasca) using carfentanil-based mixtures*, *Journal of Wildlife Diseases*, 31(1), pp. 37–42. <https://doi.org/10.7589/0090-3558-31.1.37>

Haymerle, A., Fahlman, Å., & Walzer, C. (2010), 'Human exposures to immobilising agents: results of an online survey', *The Veterinary Record*, 167(9), pp. 327–332. <https://doi.org/10.1136/vr.c4191>

Henriksen, G., Platzer, S., Marton, J., Hauser, A., Berthele, A., Schwaiger, M., et al. (2005), 'Syntheses, biological evaluation, and molecular modeling of ¹⁸F-labeled 4-anilidopiperidines as μ -opioid receptor imaging agents', *Journal of Medicinal Chemistry*, 48(24), pp. 7720–7732.

Hirvonen, J., Aalto, S., Hagelberg, N., Maksimow, A., Ingman, K., Oikonen, V., et al. (2009), 'Measurement of central μ -opioid receptor binding *in vivo* with PET and [¹¹C]carfentanil: a test–retest study in healthy subjects', *European Journal of Nuclear Medicine and Molecular Imaging*, 36(2), pp. 275–286.

Howard, L. L., Kearns, K. S., Clippinger, T. L., Larsen, R. S., & Morris, P. J. (2004), 'Chemical immobilization of rhebok (*Pelea capreolus*) with carfentanil-xylazine or etorphine-xylazine', *Journal of Zoo and Wildlife Medicine*, 35(3), pp. 312–319. <https://doi.org/10.1638/03-090>

Hudson, S. (2017). Personal communication to the EMCDDA.

InterAgency Board for Equipment Standardization and Interoperability (IAB) (2017). Recommendations on selection and use of personal protective equipment and decontamination products for first responders against exposure hazards to synthetic opioids, including fentanyl and fentanyl analogues. <https://www.interagencyboard.org/sites/default/files/publications/IAB%20First%20Responder%20PPE%20and%20Decontamination%20Recommendations%20for%20Fentanyl.pdf>

International Narcotics Control Board (INCB) (2017). INCB: Scheduling of fentanyl precursors comes into force. 18 October 2017. Available at: https://www.incb.org/incb/en/news/press-releases/2017/press_release_20171018.html

Jacobson, A. (1988), 'Biological evaluation of compounds for their physical dependence potential and abuse liability. XII.', *Drug Testing Program of the Committee on Problems of Drug Dependence, Inc.* National Institute on Drug Abuse Research Monograph, 90, pp. 392–420. <https://archives.drugabuse.gov/pdf/monographs/90.pdf>

Janssen, P. A. J. (1982), 'Potent, new analgesics, tailor-made for different purposes' *Acta Anaesthesiologica Scandinavica*, 26(3), pp. 262–268.

Janssen, P. A., & Van Daele, P. G. (1979). US Patent 4,179,569.

Jessup, D. A., Clark, W. E., Jones, K. R., Clark, R., & Lance, W. R. (1985), 'Immobilization of free-ranging desert bighorn sheep, tule elk, and wild horses, using carfentanil and xylazine: reversal with naloxone, diprenorphine, and yohimbine', *Journal of the American Veterinary Medical Association*, 187(11), pp. 1253–1254.

Jewett, D. M. (2001), 'A simple synthesis of [11C]carfentanil using an extraction disk instead of HPLC', *Nuclear Medicine and Biology*, 28(6), pp. 733–734.

Jewett, D. M., & Kilbourn, M. R. (2004), 'In vivo evaluation of new carfentanil-based radioligands for the mu opiate receptor', *Nuclear Medicine and Biology*, 31(3), pp. 321–325. <https://doi.org/10.1016/j.nucmedbio.2003.10.009>

Karesh, W. B., Uhart, M. M., Dierenfeld, E. S., Braselton, W. E., Torres, A., House, C., Cook, R. A. (1998). 'Health evaluation of free-ranging guanaco (*Lama guanicoe*)', *Journal of Zoo and Wildlife Medicine*, 29(2), pp. 134–141.

Kearns, K. S., Swenson, B., & Ramsay, E. C. (1999), 'Dosage trials with transmucosal carfentanil citrate in non-human primates', *Zoo Biology*, 18(5), pp. 397–402. [https://doi.org/10.1002/\(SICI\)1098-2361\(1999\)18:5<397::AID-ZOO4>3.0.CO;2-U](https://doi.org/10.1002/(SICI)1098-2361(1999)18:5<397::AID-ZOO4>3.0.CO;2-U)

Kearns, K. S., Swenson, B., & Ramsay, E. C. (2000), 'Oral induction of anesthesia with droperidol and transmucosal carfentanil citrate in chimpanzees (*Pan troglodytes*)', *Journal of Zoo and Wildlife Medicine*, 31(2), pp. 185–189. [https://doi.org/10.1638/1042-7260\(2000\)031\[0185:OIOAWD\]2.0.CO;2](https://doi.org/10.1638/1042-7260(2000)031[0185:OIOAWD]2.0.CO;2)

Kilgallon, C. P., Lamberski, N., & Larsen, R. S. (2010), 'Comparison of thiafentanil-xylazine and carfentanil-xylazine for immobilization of gemsbok (*Oryx gazella*)' *Journal of Zoo and Wildlife Medicine* : Official Publication of the American Association of Zoo Veterinarians, 41(3), pp. 567–571. <https://doi.org/10.1638/2010-0021.1>

Kim, H. K. and Nelson, L.S. (2015), 'Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review', *Expert Opinion on Drug Safety*, 14(7), pp. 1137–1146. <https://doi.org/10.1517/14740338.2015.1037274>

Klar, S. A., Brodtkin, E., Gibson, E., Padhi, S., Predy, C., Green, C. and Lee, V. (2016), 'Fentanyl-fentanyl overdose events caused by smoking contaminated crack cocaine — British Columbia, Canada, July 15–18, 2016', *MMWR. Morbidity and Mortality Weekly Report*, 65(37), pp. 1015–1016.

Kock, M. D., & Berger, J. (1987), 'Chemical immobilization of free-ranging North American bison (*Bison bison*) in Badlands National Park, South Dakota', *Journal of Wildlife Diseases*, 23(4), pp. 625–633.

Kreeger, T. J., Bjornlie, D., Thompson, D., Clapp, J., Clark, C., Hansen, C., Lockwood, S. (2013), 'Immobilization of Wyoming bears using carfentanil and xylazine', *Journal of Wildlife Diseases*, 49(3), pp. 674–678. <https://doi.org/10.7589/2012-10-269>

Kreeger, T. J., & Kellie, K. A. (2012), 'Sufentanil citrate immobilization of Alaskan moose calves', *Journal of Wildlife Diseases*, 48(4), pp. 1088–1091. <https://doi.org/10.7589/2012-04-112>

Kreeger, T. J., & Seal, U. S. (1990), 'Immobilization of gray wolves (*Canis lupus*) with sufentanil citrate', *Journal of Wildlife Diseases*, 26(4), pp. 561–563. <https://doi.org/10.7589/0090-3558-26.4.561>

Kuip, E. J. M., Zandvliet, M. L., Koolen, S. L. W., Mathijssen, R. H. J., & van der Rijt, C. C. D. (2017), 'A review of factors explaining variability in fentanyl pharmacokinetics; focus on implications for cancer patients', *British Journal of Clinical Pharmacology*, 83(2), pp. 294–313. <https://doi.org/10.1111/bcp.13129>

Kupper, W., Drager, N., Mehltitz, D., & Zillmann, U. (1981), 'On the immobilization of hartebeest and kob in Upper Volta', *Tropenmedizin und Parasitologie*, 32(1), pp. 58–60.

Labroo, R. B., Paine, M. F., Thummel, K. E., & Kharasch, E. D. (1997), 'Fentanyl metabolism by human hepatic and intestinal Cytochrome P450 3A4: Implications for interindividual variability in disposition, efficacy, and drug interactions', *Drug Metabolism and Disposition*, 25(9), pp. 1072–1080.

Leysen, J. E., & Gommeren, W. (1986), 'Drug-receptor dissociation time, new tool for drug research: Receptor binding affinity and drug-receptor dissociation profiles of serotonin-S2, dopamine-D2, histamine-H1 antagonists, opiates', *Drug Development Research*, 8(1-4), pp. 119–131.

Leysen, J. E., & Laduron, P. M. (1978), 'Receptor binding properties *in vitro* and *in vivo* of some long-acting opiates' *Archives Internationales de Pharmacodynamie et de Thérapie*, 232(2), pp. 243–246.

Leysen, J., Tollenaere, J. P., Koch, M. H. J., & Laduron, P. (1977), 'Differentiation of opiate and neuroleptic receptor binding in rat brain', *European Journal of Pharmacology*, 43(), pp. 253–267.

Lian, M., Beckmen, K. B., Bentzen, T. W., Demma, D. J., & Arnemo, J. M. (2016), 'Thiafentanil—azaperone—xylazine and carfentanil—xylazine immobilizations of free-ranging caribou (*Rangifer tarandus granti*) in Alaska United States' *Journal of Wildlife Diseases*, 52(2), pp. 327–334. <https://doi.org/10.7589/2015-04-101>

Lu, Z. Y., Zhao, S. Y., Yuan, X. M., & Yang, Y. L. (1990), 'Synthesis and analgesic activity of 4-N-propionyl analogs of 4-methoxycarbonyl fentanyl', *Acta Pharmaceutica Sinica*, 25(5), pp. 336–339.

Lurie, I. S., Berrier, A. L., Casale, J. F., Iio, R., & Bozenko, J. S. (2012), 'Profiling of illicit fentanyl using UHPLC–MS/MS' *Forensic Science International*, 220(1–3), pp. 191–196. <https://doi.org/10.1016/j.forsciint.2012.02.024>

Lust, E. B., Barthold, C., Malesker, M. A., & Wichman, T. O. (2011), 'Human health hazards of veterinary medications: information for emergency departments', *The Journal of Emergency Medicine*, 40(2), pp. 198–207. <https://doi.org/10.1016/j.jemermed.2009.09.026>

Lynch, M. J., Suyama, J., & Guyette, F. X. (2017), 'Scene safety and force protection in the era of ultra-potent opioids', *Prehospital Emergency Care*, pp. 1–6. <https://doi.org/10.1080/10903127.2017.1367446>

Lynch, M., Mohny, S., & Shulman, J. (2017), 'Postmortem analysis of carfentanil associated overdose deaths', *Clinical Toxicology*, (Philadelphia, Pa.), 55(7), p. 785.

Maguire, P., Tsai, N., Kamal, J., Cometta-Morini, C., Upton, C., & Loew, G. (1992), 'Pharmacological profiles of fentanyl analogs at μ , δ and κ opiate receptors', *European Journal of Pharmacology*, 213(2), pp. 219–225. [https://doi.org/http://dx.doi.org/10.1016/0014-2999\(92\)90685-W](https://doi.org/http://dx.doi.org/10.1016/0014-2999(92)90685-W)

Malaquin, S., Jida, M., Gesquiere, J. C., Deprez-Poulain, R., Deprez, B., & Laconde, G. (2010), 'Ugi reaction for the synthesis of 4-aminopiperidine-4-carboxylic acid derivatives. Application to the synthesis of carfentanil and remifentanil', *Tetrahedron Letters*, 51(22), pp. 2983–2985. <https://doi.org/10.1016/j.tetlet.2010.03.120>

- Mao, C.-L., Zientek, K. D., Colahan, P. T., Kuo, M.-Y., Liu, C.-H., Lee, K.-M., & Chou, C.-C. (2006), 'Development of an enzyme-linked immunosorbent assay for fentanyl and applications of fentanyl antibody-coated nanoparticles for sample preparation', *Journal of Pharmaceutical and Biomedical Analysis*, 41(4), pp. 1332–1341. <https://doi.org/10.1016/j.jpba.2006.03.009>
- Marton, J., Glaenzel, B., Roessler, J., Golaszewski, D., & Henriksen, G. (2012), 'A convenient route to 4-carboxy-4-anilidopiperidine esters and acids', *Molecules* (Basel, Switzerland), 17(3), pp. 2823–2832. <https://doi.org/10.3390/molecules17032823>
- Maryanoff, B. E., Simon, E. J., Gioannini, T., & Gorissen, H. (1982), 'Potential affinity labels for the opiate receptor based on fentanyl and related compounds' *Journal of Medicinal Chemistry*, 25(8), pp. 903–19.
- Massey, J., Kilkenny, M., Batdorf, S., Sanders, S. K., Ellison, D., Halpin, J., Gupta, R. (2017), 'Opioid overdose outbreak - West Virginia, August 2016', *MMWR. Morbidity and Mortality Weekly Report*, 66(37), pp. 975–980. <https://doi.org/10.15585/mmwr.mm6637a3>
- Macleod, D. B., Habib, A. S., Ikeda, K., Spyker, D. A., Cassella, J. V., Ho, K. Y., Gan, T. J. (2012), 'Inhaled fentanyl aerosol in healthy volunteers: pharmacokinetics and pharmacodynamics', *Anesthesia and Analgesia*, 115(5), pp. 1071–1077. <https://doi.org/10.1213/ANE.0b013e3182691898>
- Meuldermans, W. E., Hurkmans, R. M., & Heykants, J. J. (1982), 'Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood', *Archives Internationales de Pharmacodynamie et de Therapie*, 257(1), pp. 4–19. <http://www.ncbi.nlm.nih.gov/pubmed/6214227>
- Mićović, I. V., Ivanović, M. D., Vučković, S., Jovanović-Mićić, D., Beleslin, D., Došen-Mićović, L., & Kiricojević, V. D. (1998), '3-Carbomethoxy fentanyl: Synthesis, pharmacology and conformational analysis' *Heterocyclic Communications*, 4(2), pp. 171–179. <https://doi.org/10.1515/HC.1998.4.2.171>
- Miller, B. F., Muller, L. I., Storms, T. N., Ramsay, E. C., Osborn, D. A., Warren, R. J., Adams, K. A. (2003), 'A comparison of carfentanil/xylazine and Telazol/xylazine for immobilization of white-tailed deer' *Journal of Wildlife Diseases*, 39(4), pp. 851–858. <https://doi.org/10.7589/0090-3558-39.4.851>
- Miller, M. W., Wild, M. A., & Lance, W. R. (1996), 'Efficacy and safety of naltrexone hydrochloride for antagonizing carfentanil citrate immobilization in captive Rocky Mountain elk (*Cervus elaphus nelsoni*)', *Journal of Wildlife Diseases*, 32(2), pp. 234–239. <https://doi.org/10.7589/0090-3558-32.2.234>
- Minkowski, C. P., Epstein, D., Frost, J. J., & Gorelick, D. A. (2012), 'Differential response to IV carfentanil in chronic cocaine users and healthy controls', *Addiction Biology*, 17(1), pp. 149–155. <https://doi.org/10.1111/j.1369-1600.2010.00256.x>
- Moffat, A. C., Osselton, M. D., Widdop, B., et al. (eds) (2016). 'Clarke's Analysis of Drugs and Poisons', *Pharmaceutical Press*, London, Fentanyl Monograph. https://www.medicinescomplete.com/mc/clarke/current/c-d1e495336.htm?q=fentanyl&t=search&ss=text&tot=63&p=1_-_hit.

- Moresco, A., Larsen, R. S., Sleeman, J. M., Wild, M. A., & Gaynor, J. S. (2001), 'Use of naloxone to reverse carfentanil citrate-induced hypoxemia and cardiopulmonary depression in Rocky Mountain wapiti (*Cervus elaphus nelsoni*)' *Journal of Zoo and Wildlife Medicine*, 32(1), pp. 81–89. [https://doi.org/10.1638/1042-7260\(2001\)032\[0081:UONTRC\]2.0.CO;2](https://doi.org/10.1638/1042-7260(2001)032[0081:UONTRC]2.0.CO;2)
- Mortenson, J. (1994). American Association of Zoo Veterinarians Annual Conference. In Oral carfentanil citrate use in white-handed gibbons (*Hylobates lar*). p. 163.
- Mortenson, J., & Bechert, U. (2001), 'Carfentanil citrate used as an oral anesthetic agent for brown bears (*Ursus arctos*)' *Journal of Zoo and Wildlife Medicine*, Official Publication of the American Association of Zoo Veterinarians, 32(2), pp. 217–221. [https://doi.org/10.1638/1042-7260\(2001\)032\[0217:CCUAAO\]2.0.CO;2](https://doi.org/10.1638/1042-7260(2001)032[0217:CCUAAO]2.0.CO;2)
- Moss, M. J., Warrick, B. J., Nelson, L. S., McKay, C. A., Dubé, P-A., Gosselin, S., Palmer, R. B. and Stolbach, A. I. (2017), 'ACMT and AACT position statement: preventing occupational fentanyl and fentanyl analog exposure to emergency responders', *Clinical Toxicology (Philadelphia)*. <https://doi.org/10.1007/s13181-017-0628-2>
- Müller, S., Nussbaumer, S., Plitzko, G., Ludwig, R., Weinmann, W., Krahenbuhl, S., & Liakoni, E. (2017), 'Recreational use of carfentanil - a case report with laboratory confirmation', *Clinical Toxicology (Philadelphia, Pa.)*, pp. 1–2. <https://doi.org/10.1080/15563650.2017.1355464>
- Müller, S., Nussbaumer, S., Plitzko, G., Ludwig, R., Weinmann, W., & Liakoni, E. (2017), 'Recreational carfentanil : the devil in disguise', *Clinical Toxicology (Philadelphia, Pa.)*, 55(5), p. 451.
- Mutlow, A., Isaza, R., Carpenter, J. W., Koch, D. E., & Hunter, R. P. (2004), 'Pharmacokinetics of carfentanil and naltrexone in domestic goats (*Capra hircus*)', *Journal of Zoo and Wildlife Medicine*, 35(4), pp. 489–496. <https://doi.org/10.1638/03-074>
- Napier, J. E., Loskutoff, N. M., Simmons, L. G., & Armstrong, D. L. (2011), 'Comparison of carfentanil-xylazine and thiafentanil-medetomidine in electroejaculation of captive gaur (*Bos gaurus*)' *Journal of Zoo and Wildlife Medicine*, 42(3), pp. 430–436. <https://doi.org/10.1638/2010-0242.1>
- Newberg, A. B., Ray, R., Scheuermann, J., Wintering, N., Saffer, J., Schmitz, A., et al. (2009), 'Dosimetry of ¹¹C-carfentanil, a μ -opioid receptor imaging agent' *Nuclear Medicine Communications*, 30(4), pp. 314–318.
- Olives, T., Love, S., Meyers, S., Wilcoxon, R., Kloss, J., & Cole, J. (2017), 'Sentinel carfentanil deaths in a midwestern state: findings and interagency response', *Clinical Toxicology (Philadelphia, Pa.)*, 55(7), pp. 830–831.
- Papsun, D., Isenschmid, D., & Logan, B. K. (2017), 'Observed carfentanil concentrations in 355 blood specimens from forensic investigations', *Journal of Analytical Toxicology*. <https://doi.org/10.1093/jat/bkx068>
- Pattinson, K. T. (2008), 'Opioids and the control of respiration', *British Journal of Anaesthesia*, 2008, 100, pp. 747–758. <https://doi.org/10.1093/bja/aen094>

Perrine, T. D., Atwell, L., Tice, I. B., Jacobson, A. E. and May, E. L. (1972), 'Analgesic activity as determined by the Nilsen method', *Journal of Pharmaceutical Sciences*, 61(1), pp. 86–8.
<http://dx.doi.org/10.1002/jps.2600610115>

Pollock, C. G., & Ramsay, E. C. (2003), 'Serial immobilization of a Brazilian tapir (*Tapirus terrestris*) with oral detomidine and oral carfentanil', *Journal of Zoo and Wildlife Medicine*, 34(4), pp. 408–410.
<https://doi.org/10.1638/01-061>

Portas, T. J. (2004), 'A review of drugs and techniques used for sedation and anaesthesia in captive rhinoceros species', *Australian Veterinary Journal*, 82(9), pp. 542–549.

Raath, J. P., Quandt, S. K. F., & Malan, J. H. (1992), 'Ostrich (*Struthio camelus*) immobilisation using carfentanil and xylazine and reversal with yohimbine and naltrexone', *Journal of the South African Veterinary Association*, 63(4), pp. 138–140.

Rainwater, K. L., Valitutto, M. T., Kalk, P., Moore, R. P., & Sykes, J. M. (2013), 'Comparison of two injectable immobilization combinations in Himalayan tahr (*Hemitragus jemlahicus*): medetomidine, ketamine, and atipamezole versus carfentanil, xylazine, naltrexone, and atipamezole', *Journal of Zoo and Wildlife Medicine*, Official Publication of the American Association of Zoo Veterinarians, 44(3), pp. 596–604.
<https://doi.org/10.1638/2012-0140R1.1>

Ramsay, E. C., Sleeman, J. M., & Clyde, V. L. (1995), 'Immobilization of black bears (*Ursus americanus*) with orally administered carfentanil citrate', *Journal of Wildlife Diseases*, 31(3), pp. 391–393.
<https://doi.org/10.7589/0090-3558-31.3.391>

Reiff, L. P., Sollman, P. B. (1992), 'Process making carfentanil and related analgesics'. United States patent 5,106,983.

Riches, J. R., Read, R. W., Black, R. M., Cooper, N. J., & Timperley, C. M. (2012), 'Analysis of clothing and urine from Moscow theatre siege casualties reveals carfentanil and remifentanil use', *Journal of Analytical Toxicology*, 36(9), pp. 647–656. <https://doi.org/10.1093/jat/bks078>

Rittgen, J., Pütz, M., & Zimmermann, R. (2012), 'Identification of fentanyl derivatives at trace levels with nonaqueous capillary electrophoresis-electrospray-tandem mass spectrometry (MS(n), n = 2, 3): Analytical method and forensic applications', *Electrophoresis*, 33(11), pp. 1595–1605.
<https://doi.org/10.1002/elps.201100655>

Rodríguez, D., Urrutia, G., Escobar, Y., Moya, J., & Murillo, M. (2015), 'Efficacy and safety of oral or nasal fentanyl for treatment of breakthrough pain in cancer patients: A systematic review', *Journal of Pain & Palliative Care Pharmacotherapy*, 29(3), pp. 228–246. <https://doi.org/10.3109/15360288.2015.1047554>

Saari, T. I., Laine, K., Neuvonen, M., Neuvonen, P. J., & Olkkola, K. T. (2008), 'Effect of voriconazole and fluconazole on the pharmacokinetics of intravenous fentanyl', *European Journal of Clinical Pharmacology*, 64(1), pp. 25–30. <https://doi.org/10.1007/s00228-007-0398-x>

Saji, H., Tsutsumi, D., Magata, Y., Iida, Y., Konishi, J., & Yokoyama, A. (1992), 'Preparation and biodistribution in mice of [^{11}C]carfentanil: a radiopharmaceutical for studying brain mu-opioid receptors by positron emission tomography', *Annals of Nuclear Medicine*, 6(1), pp. 63–67.

San Francisco Department of Public Health (SFDPH) (2015). Severe opioid overdoses in San Francisco caused by fentanyl-containing "Xanax" pill. 10-22-2015. Available at: <http://www.sfdcp.org/document.html?id=1005>

Schumacher, J., Citino, S. B., & Dawson, R. J. (1997), 'Effects of a carfentanil-xylazine combination on cardiopulmonary function and plasma catecholamine concentrations in female bongo antelopes', *American Journal of Veterinary Research*, 58(2), pp. 157–161.

Schumacher, J., Heard, D. J., Young, L., & Citino, S. B. (1997), 'Cardiopulmonary effects of carfentanil in dama gazelles (*Gazella dama*)', *Journal of Zoo and Wildlife Medicine*, 28(2), pp. 166–170.

Seal, U. S., Schmitt, S. M., & Peterson, R. O. (1985), 'Carfentanil and xylazine for immobilization of moose (*Alces alces*) on Isle Royale', *Journal of Wildlife Diseases*, 21(1), pp. 48–51.

Seither, J., & Reidy, L. (2017), 'Confirmation of Carfentanil, U-47700 and other synthetic opioids in a human performance case by LC–MS–MS', *Journal of Analytical Toxicology*, 41(6), pp. 493–497. <http://dx.doi.org/10.1093/jat/bkx049>

Shanks, K. G., & Behonick, G. S. (2017), 'Detection of carfentanil by LC-MS-MS and reports of associated fatalities in the USA', *Journal of Analytical Toxicology*, 41(6), pp. 466–472. <https://doi.org/10.1093/jat/bkx042>

Shao, X., Fawaz, M. V., Jang, K., & Scott, P. J. H. (2014), 'Ethanol carbon-11 chemistry: The introduction of green radiochemistry', *Applied Radiation and Isotopes*, 89, pp. 125–129. <https://doi.org/10.1016/j.apradiso.2014.01.033>

Shao, X., Hoareau, R., Runkle, A. C., Tluczek, L. J. M., Hockley, B. G., Henderson, B. D., & Scott, P. J. H. (2011), 'Highlighting the versatility of the Tracerlab synthesis modules. Part 2: fully automated production of [^{11}C]-labeled radiopharmaceuticals using a Tracerlab FXC-Pro', *Journal of Labelled Compounds and Radiopharmaceuticals*, 54(14), pp. 819–838. <https://doi.org/10.1002/jlcr.1937>

Shao, X., & Kilbourn, M. R. (2009), 'A simple modification of GE tracerlab FX C Pro for rapid sequential preparation of [^{11}C]carfentanil and [^{11}C]raclopride', *Applied Radiation and Isotopes*, 67(4), pp. 602–605. <https://doi.org/10.1016/j.apradiso.2008.12.013>

Shaw, M. L., Carpenter, J. W., & Leith, D. E. (1995), 'Complications with the use of carfentanil citrate and xylazine hydrochloride to immobilize domestic horses', *Journal of the American Veterinary Medical Association*, 206(6), pp. 833–836.

Shoff, E. N., Zaney, M. E., Kahl, J. H., Hime, G. W., & Boland, D. M. (2017), 'Qualitative Identification identification of fentanyl analogs and other opioids in post-mortem cases by UHPLC-Ion Trap-MSn', *Journal of Analytical Toxicology*, 41(6), pp. 484–492. <https://doi.org/10.1093/jat/bkx041>

Shulman, J., Nunnally, B., Marino, R., & Lynch, M. (2017), 'Laboratory confirmed intravenous carfentanil exposure requiring naloxone infusion', *Clinical Toxicology* (Philadelphia, Pa.), 55(7), pp. 787–788.

Shury, T. K., Caulkett, N. A., & Woodbury, M. R. (2010), 'Intranasal naltrexone and atipamezole for reversal of white-tailed deer immobilized with carfentanil and medetomidine', *The Canadian Veterinary Journal*, 51(5), pp. 501–505.

Siegfried. (n.d.). Synthesis of fentanyl - [www.rhodium.ws]. Retrieved September 11, 2017. Available from <https://erowid.org/archive/rhodium/chemistry/fentanyl.html>

Sleeman, J. M., Carter, W., Tobin, T., & Ramsay, E. C. (1997), 'Immobilization of domestic goats (*Capra hircus*) using orally administered carfentanil citrate and detomidine hydrochloride', *Journal of Zoo and Wildlife Medicine*, 28(2), pp. 158–165.

Sofalvi, S., Schueler, H. E., Lavins, E. S., Kaspar, C. K., Brooker, I. T., Mazzola, C. D., Perch, S. (2017), 'An LC–MS–MS method for the analysis of carfentanil, 3-methylfentanyl, 2-furanyl fentanyl, acetyl fentanyl, fentanyl and norfentanyl in post-mortem and impaired-driving cases', *Journal of Analytical Toxicology*, 41(6), pp. 473–483. <https://doi.org/10.1093/jat/bkx052>

Stanley, T. (2003), 'Human immobilization: is the experience in Moscow just the beginning?', *European Journal of Anaesthesiology*, 20(6), pp. 427–428.

Stanley, T. H., Egan, T. D., & Van Aken, H. (2008), 'A tribute to Dr. Paul A. J. Janssen: entrepreneur extraordinaire, innovative scientist, and significant contributor to anesthesiology', *Anesthesia and Analgesia*, 106(2), pp. 451–462. <https://doi.org/10.1213/ane.0b013e3181605add>

Storms, T. N., Schumacher, J., Osborn, D. A., Miller, K. V., & Ramsay, E. C. (2006), 'Effects of ketamine on carfentanil and xylazine immobilization of white-tailed deer (*Odocoileus virginianus*)', *Journal of Zoo and Wildlife Medicine*, 37(3), pp. 347–353. <https://doi.org/10.1638/05-079.1>

Storms, T. N., Schumacher, J., Zagaya, N., Osborn, D. A., Miller, K. V., & Ramsay, E. C. (2005), 'Determination and evaluation of an optimal dosage of carfentanil and xylazine for the immobilization of white-tailed deer (*Odocoileus virginianus*)', *Journal of Wildlife Diseases*, 41(3), pp. 559–568. <https://doi.org/10.7589/0090-3558-41.3.559>

Somerville, N. J., O'Donnell, J., Gladden, R. M., Zibbell, J. E., Green, T. C., Younkin, M., Ruiz, S., Babakhanlou-Chase, H., Chan, M., Callis, B. P., Kuramoto-Crawford, J., Nields, H. M., Walley, A. Y., (2017), 'Characteristics of fentanyl overdose - Massachusetts, 2014–2016', *MMWR. Morbidity and Mortality Weekly Report*, 66(14), pp. 382–386. <https://doi.org/10.15585/mmwr.mm6614a2>

Sutter, M. E., Gerona, R. R., Davis, M. T., Roche, B. M., Colby, D. K., Chenoweth, J. A., Adams, A. J., Owen, K. P., Ford, J. B., Black, H. B. and Albertson, T. E. (2017), 'Fatal fentanyl: one pill can kill', *Academic Emergency Medicine*, 24(1), pp. 106–113.

Swanson, D. M., Hair, L. S., Strauch Rivers, S. R., Smyth, B. C., Brogan, S. C., Ventoso, A. D., Pearson, J. M. (2017), 'Fatalities involving carfentanil and furanyl fentanyl: Two case reports'. *Journal of Analytical Toxicology*, 41(6), pp. 498-502. <https://doi.org/10.1093/jat/bkx037>

Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) (2016) Monograph. Carfentanil. Available at: <http://www.swgdrug.org/Monographs/Carfentanil.pdf>

Taber, D. F., & Rahimizadeh, M. (1992), 'Amide to ester conversion: a practical route to the carfentanil class of analgesics', *Journal of Organic Chemistry*, 57(14), pp. 4037-4038.

Thompson, R.G., Menking, D., & Valdes. J. J. (1987). Opiate receptor binding properties of carfentanil. Report. Aberdeen Proving Ground, Maryland: Chemical Research Development & Engineering Center; Report No.: AD-A187 637. Available at: <http://www.dtic.mil/dtic/tr/fulltext/u2/a187637.pdf>

Titeler, M., Lyon, R. A., Kuhar, M. J., Frost, J. F., Dannals, R.F., Leonhardt, S., et al. (1989), 'm Opiate receptors are selectively labelled by [3H]carfentanil in human and rat brain' *European Journal of Pharmacology*, 167(2), pp. 221–228.

Tollenaere, J. P., Moereels, H., Van Loon, M. (1986), 'On conformation analysis, molecular graphics, fentanyl and its derivatives' in: Jucker, E, (Ed.) *Progress in Drug Research*, Birkhauser Verlag, Basel, pp. 91–126.

Tomassoni, J., Hawk, K. F., Jubanyik, K., Nogee, D. P., Durant, T., Lynch, K. L., Patel, R., Dinh, D., Ulrich, A. and D'Onofrio G. (2017), 'Multiple fentanyl overdoses - New Haven, Connecticut, June 23, 2016', *MMWR. Morbidity and Mortality Weekly Report*, 66(4), pp. 107–111.

Toronto Research Chemicals Inc. (2011). Carfentanil MSDS. <https://www.trc-canada.com/prod-img/MSDS/C183480MSDS.pdf>

Ujváry, R. Jorge, R. Christie, T. Le Ruez, H. V. Danielsson, R. Kronstrand, S. Elliott, A. Gallegos, R. Sedefov, and M. Evans-Brown. (2017), 'Acryloylfentanyl, a recently emerged new psychoactive substance: a comprehensive review', *Forensic Toxicology*, 35(2), pp. 232–243.

United States Centers for Disease Control and Prevention (US CDC) (2013). Recommendations for laboratory testing for acetyl fentanyl and patient evaluation and treatment for overdose with synthetic opioid, 20 June 2013. <https://emergency.cdc.gov/han/han00350.asp>.

United States Centers for Disease Control and Prevention (US CDC) (2016). Fentanyl: Preventing occupational exposure to emergency responders, November 28, 2016.
<https://www.cdc.gov/niosh/topics/fentanyl/default.html>

United States Drug Enforcement Administration (US DEA) (2017). Fentanyl. A briefing guide for first responders. U.S. Drug Enforcement Administration
https://www.dea.gov/druginfo/Fentanyl_BriefingGuideforFirstResponders_June2017.pdf

United States Food and Drug Administration (US FDA) (n.d.). WILDNIL - NADA 139-633. FDA Freedom of Information Summary (Vol. 111).

Van Bever, W. F. M., Niemegeers, C. J. E., Schellekens, K. H. L., & Janssen, P. A. J. (1976), 'N-4-Substituted 1-(2-arylethyl)-4-piperidiny-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin', *Arzneimittel-Forschung*, 26(8), pp. 1548–1551.
<http://www.ncbi.nlm.nih.gov/pubmed/12771>

Van Daele, P. G. H., De Bruyn, M. F. L., Boey, J. M., Sanczuk, S., Agten, J. T. M., & Janssen, P. A. J. (1976), 'Synthetic analgesics: N-(1-[2-arylethyl]-4-substituted 4-piperidiny) N-arylalkanamides', *Arzneimittel-Forschung*, 26(8), pp. 1521–31. <http://www.ncbi.nlm.nih.gov/pubmed/12769>

van der Schrier, R., Roozekrans, M., Olofsen, E., Aarts, L., van Velzen, M., de Jong, M., Dahan, A., Niesters M. (2017), 'Influence of ethanol on oxycodone-induced respiratory depression: A dose-escalating study in young and elderly individuals', *Anesthesiology*, 126(3), pp. 534–542.

Villemagne, V. L., Frost, J. J., Dannals, R. F., Lever, J. R., Tanada, S., Natarajan, T. K., Wagner, H. N. Jr. (1994), 'Comparison of [¹¹C]diprenorphine and [¹¹C]carfentanil *in vivo* binding to opiate receptors in man using a dual detector system', *European Journal of Pharmacology*, 257(1–2), pp. 195–197.

Walsh, V. P., & Wilson, P. R. (2002), 'Sedation and chemical restraint of deer', *New Zealand Veterinary Journal*, 50(6), pp. 228–236. <https://doi.org/10.1080/00480169.2002.36318>

Walz, A. J., Hsu, F.-L.. (2014), 'Synthesis of 4-anilinopiperidine methyl esters, intermediates in the production of carfentanil, sufentanil, and remifentanil' *Tetrahedron Letters*, 55(2), pp. 501–502.

Wang, L., & Bernert, J. T. (2006), 'Analysis of 13 fentanils, including sufentanil and carfentanil, in human urine by liquid chromatography-atmospheric-pressure ionization-tandem mass spectrometry', *Journal of Analytical Toxicology*, 30(5), pp. 335–341.

Wang, H., Zhang, Z., Liu, P., Xue, F., Zuo, C., Hua, F., Huang, Z., Zhao, J., & Guan, Y. (2011), 'Synthesis of opiate receptor radioligand ¹¹C-carfentanil and its biodistribution in rats', *Chinese Journal of Nuclear Medicine*, 31(1), pp. 46–49.

Wax, P. M., Becker, C. E., & Curry, S. C. (2003), 'Unexpected 'gas ' casualties in Moscow: a medical toxicology perspective', *Annals of Emergency Medicine*, 41(5), pp. 700–705.
<https://doi.org/10.1067/mem.2003.148>

Wen, S. T., Yang, Y. L., Shao, H. Z., Zhang, K. G., Li, Y. L., Chen, J. S. (1993), 'Synthesis and analgesic activity of non-aryl analogues of 4-methoxycarbonyl fentanyl', *Acta Pharmaceutica Sinica*, 28(3), pp. 181–187.

White, J. M. and Irvine, R. J. (1999), 'Mechanisms of fatal opioid overdose', *Addiction*, 94(7), pp. 961–972.
<https://doi.org/10.1046/j.1360-0443.1999.9479612.x>

Wynn, R. L., Ford, R. D., McCourt, P. J., Ramkumar, V., Bergman, S. A., & Rudo, F. G. (1986), 'Rabbit tooth pulp compared to 55°C mouse hot plate assay for detection of antinociceptive activity of opiate and nonopiate central analgesics', *Drug Development Research*, 9, pp. 233–239.

Wong, B., Perkins, M. W., Tressler, J., Rodriguez, A., Devorak, J., & Sciuto, A. M. (2017), 'Effects of inhaled aerosolized carfentanil on real-time physiological responses in mice: a preliminary evaluation of naloxone', *Inhalation Toxicology*, 29(2), pp. 65–74. <https://doi.org/10.1080/08958378.2017.1282065>

Woods, J., Medzihradsky, F., Smith, C., G, W., & France, C. (1988), 'Evaluation of new compounds for opioid activity', *National Institute on Drug Abuse Research Monograph*, 90, pp. 421–467.
<https://archives.drugabuse.gov/pdf/monographs/90.pdf>

Yeaden, M.; Kitchen, I. (1988), 'Comparative binding of μ and δ selective ligands in whole brain and pons/medulla homogenates from rat: Affinity profiles of fentanyl derivatives', *Neuropharmacology*, 27(4), pp. 345–348. [https://doi.org/10.1016/0028-3908\(88\)90141-4](https://doi.org/10.1016/0028-3908(88)90141-4)

Yin, S. (2017), 'Deaths associated with carfentanil in Hamilton County, OH', *Clinical Toxicology (Philadelphia, Pa.)*, 55(7), p. 805.

Yong, Z., Gao, X., Ma, W., Dong, H., Gong, Z., & Su, R. (2014), 'Nalmefene reverses carfentanil-induced loss of righting reflex and respiratory depression in rats', *European Journal of Pharmacology*, 738, pp. 153–157. <https://doi.org/10.1016/j.ejphar.2014.05.044>

Zhang, J-M., Xu, Z-H., Zhang, X-J., Xiang, X-H., T. J.-H. (2011), 'Automated synthesis of ^{11}C -carfentanil with ^{11}C -choline module and micro PET imaging', *Tongweisu (Journal of Isotopes)*, 24(3), pp. 182–187.
<http://www.xueshu.com/tws/201103/12439883.html>



European Monitoring Centre
for Drugs and Drug Addiction

Annex 2. List of participants at the risk assessment meetings of Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil)

7-8 November 2017

A. Extended Scientific Committee

Dr Anne Line BRETTEVILLE-JENSEN

Norwegian Institute for Alcohol and Drug Research, Oslo
Chair of the Scientific Committee

Professor Dr Gerhard BUEHRINGER

Addiction Research Unit, Department of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Institut für Therapieforschung (IFT), Munich

Professor Dr Paul DARGAN

Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

Dr Marina DAVOLI

Department of Epidemiology, Lazio Regional Health Service, Rome

Professor Dr Gabriele FISCHER

Medical University Vienna, Center of Public Health, Vienna

Professor Dr Henk GARRETSEN

Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg

Professor Dr Krzysztof KRAJEWSKI

Department of Criminology, Jagiellonian University, Krakow

Dr Fernando RODRÍGUEZ de FONSECA

Fundación IMABIS, Hospital Universitario Carlos Haya de Málaga, Málaga

Professor Dr Rainer SPANAGEL

Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Dr Wim BEST

Utrecht University, Faculty of Science, Freudenthal Institute, Utrecht

Dr Simon BRANDT

School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Professor Dr Gaetano Di CHIARA

Biomedical Sciences Department, University of Cagliari, Cagliari

Professor Dr Éva KELLER

Semmelweis University, Department of Forensic and Insurance Medicine, Budapest

Dr Claude GUILLOU

Directorate F – Health, Consumers and Reference Materials, DG Joint Research Centre, European Commission

Edith HOFER

Organised Crime and Drugs Policy Unit, DG HOME, European Commission

Dr Leon Van Aerts

Section Pharmacology, Toxicology and Biotechnology, College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht, on behalf of European Medicines Agency

Werner VERBRUGGEN

Europol's Drug Unit, Europol

Paul GRIFFITHS

Scientific Director, EMCDDA

Dr Roumen SEDEFOV

Head of Unit, Supply reduction and new drugs unit, EMCDDA

B. Invited Experts

Professor Dr Volker AUWÄRTER

Freiburg University, Institute of Forensic Medicine, Freiburg

Dr Robert KRONSTRAND

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

Professor Dr Bela SZABO

Institute of Experimental and Clinical Pharmacology and Toxicology, Freiburg

Dr István UJVÁRY

Budapest University of Technology and Economics, Budapest

C. EMCDDA Staff

Anabela ALMEIDA

Action on new drugs sector, Supply reduction and new drugs unit

Rachel CHRISTIE

Action on new drugs sector, Supply reduction and new drugs unit

Michael EVANS-BROWN

Action on new drugs sector, Supply reduction and new drugs unit

Ana GALLEGOS

Action on new drugs sector, Supply reduction and new drugs unit

Rita JORGE

Action on new drugs sector, Supply reduction and new drugs unit

Joanna DE MORAIS

Action on new drugs sector, Supply reduction and new drugs unit

Sofia SOLA

Action on new drugs sector, Supply reduction and new drugs unit
