

ACMD

Advisory Council on the Misuse of Drugs

ACMD Chair: Dr Owen Bowden-Jones
ACMD NPS Committee Secretary: Imogen McHarg
4th Floor (NE), Peel Building
2 Marsham Street
London
SW1P 4DF
ACMD@homeoffice.gov.uk

Rt. Hon. Priti Patel MP
Home Secretary
2 Marsham Street
London
SW1P 4DF

Friday, 3 January 2020

Dear Home Secretary,

Re: ACMD Report – Misuse of Fentanyl and Fentanyl Analogues

In July 2017 the then-Home Secretary commissioned the Advisory Council on the Misuse of Drugs (ACMD) to consider fentanyl and fentanyl analogues following the publication of the Drug Strategy 2017.

Prompted by concerns over increasing drug-related deaths rates and growing evidence from law enforcement agencies of fentanyl entering European drug markets, this commission sought advice from the ACMD on the number and nature of known fentanyl analogues - and their known and likely risk factors.

This report includes: a literature review on the pharmacology and toxic effects of fentanyl and related analogues; details of the misuse potential of both pharmaceutical and illicitly manufactured fentanyl compounds, and, a summary of the associated harms as documented internationally and in the UK.

The Misuse of Drugs Act 1971 already contains a generic definition for fentanyls which has proved to be robust in bringing the majority of fentanyl-related analogues under legal control. Despite this, the rates of registered deaths involving fentanyl variants in the UK have increased over the past decade, with deaths likely to be under-represented, since sufficiently detailed forensic analyses are not always carried out.

Therefore, it can be concluded that fentanyl and fentanyl-analogues present a significant ongoing risk to UK public health. Current monitoring and surveillance systems should be adapted for accurate quantification and monitoring of this threat.

To summarise, the ACMD have drawn the following conclusions and recommendations from the evidence presented in this report:

Conclusions

1. Fentanyl and its analogues are potent compounds that carry a high risk of accidental overdose that may be fatal. Infiltration of fentanyls into the heroin supply chain in the United States and Canada has been responsible for substantial increases in drug-related deaths.
2. The risk to public health from fentanyls may be lower in the UK than in North America because there is a smaller population of people who have become habituated to strong opioids. There is, however, limited information available about diversion rates and misuse of pharmaceutical fentanyls in the UK.
3. Episodes of fentanyl toxicity and deaths in the UK have been sporadic and have not approached the very high numbers seen in North America. However, rates of registered deaths involving fentanyls have recently increased and may be under-estimated because sufficiently detailed forensic analysis of drug causes is sometimes not carried out. Consequently, the role of a fentanyl in the death may not be recognised.
4. There remains an ongoing risk of fentanyls and other new synthetic opioids increasingly infiltrating the UK heroin market and increasing rates of drug-related deaths. The long-standing UK generic control on fentanyls has proved to be robust and almost all 'designer' fentanyl variants being encountered are automatically controlled in the UK as Class A drugs. There are a small number that are not controlled, although these are largely of lower potency and carry a lower risk of overdose. Most fentanyl precursors are also controlled, with some exceptions.

Recommendations

1. Research should be commissioned to study diversion and non-medical use of strong opioids to identify trends, drug products involved and populations at risk.
2. Government departments should conduct a full review of international drug strategy approaches to fentanyl markets, in particular, the North American experience, and consider interdiction controls that can be applied to the UK situation.
3. Ensure that health professionals are trained in the appropriate therapeutic use of strong opioids, as described in the 'Opioids Aware' resource and the forthcoming NICE guidance on management of chronic pain.
4.
 - A) Toxicology analysis of samples of all deaths related to drug poisoning should include analysis for fentanyl and fentanyl analogues as non-systematic screening hinders our capacity to understand trends in drug death.

- B) Toxicology reports from all deaths related to drug poisoning should include a clear statement as to whether fentanyl and/or its analogues were included in the testing. Importantly, it should be made explicit if fentanyl and/or its analogues have not been tested for. This would enable meaningful monitoring of trends in fentanyl-associated deaths.
- 5.
- A) Research should be commissioned to monitor the local and national prevalence of fentanyl and fentanyl analogues in:
- i) drug seizures, including heroin preparations and counterfeit medicines
 - ii) non-fatal episodes of heroin toxicity requiring hospital treatment.
- B) Increased funding should be made available to the Defence, Science and Technology Laboratory Forensic Early Warning System (DSTL FEWS) programme to increase capacity to analyse un-adopted police and border force seizures.
6. Agencies with responsibilities relating to drugs of misuse should monitor the international situation and share available UK data. There should also be a comprehensive early warning system which has access to up to date consolidated UK-wide drug misuse data sets.
7. If materials are encountered in the UK or Europe that retain potency but fall outside the UK generic control on fentanyls, a small amendment to that generic control should be applied to address these.
8. Following a consultation with the research community the Home Office should expand the precursor controls to cover simple variants of ANPP, the immediate precursor to fentanyl (further details are included in this report).

We look forward to discussing this report with you in due course.

Yours sincerely,



Dr Owen Bowden-Jones

Chair of ACMD



Professor Simon Thomas

Chair of ACMD NPS Committee

ACMD

Advisory Council on the Misuse of Drugs

Misuse of fentanyl and fentanyl analogues

January 2020

Contents

1. Introduction.....	6
2. Background and pharmacology	7
3. Semi-synthetic and synthetic opioids.....	8
4. Pharmaceutical fentanyls.....	9
5. Clinical effects.....	12
6. Non-medical use of pharmaceutical fentanyls	13
7. Illicitly manufactured synthetic opioids.....	15
8. Illicit fentanyl analogues.....	16
9. Synthetic opioids in North America	19
10. North American initiatives in response to synthetic opioids	21
11. Synthetic Opioids in Europe	24
12. Synthetic Opioids in the UK.....	25
13. UK Law Enforcement.....	33
14. Legal status of fentanyls - UK.....	35
15. Conclusions	36
16. Recommendations.....	36
Annex 1: Primary care prescribing (prescription numbers) of fentanyl products in England, 2014-2018 (NHS Digital, 2019)	40
Annex 2: NPIS data on fentanyls, fentanyl analogues and other new synthetic opioids.....	41
Annex 3: Fentanyl analogues notified in the EMCDDA EU Early Warning System on new psychoactive substances, 2013-2019.....	42
Annex 4: ACMD recommendations for reducing opioid-related deaths in the UK (December 2016)	43
Annex 5: International legal status of fentanyls	44
Annex 6. Fentanyl precursor controls.....	48
Annex 7. Comparative potencies of fentanyl variants.....	50
Annex 8 – List of Abbreviations used in this report	54
Annex 9 – ACMD membership, at time of publication	56
Annex 10 – ACMD NPS Committee membership.....	58
References.....	60

1. Introduction

1.1. Fentanyl is a licensed medicine used for anaesthesia and pain management. Like morphine, heroin, codeine and other 'opioid' drugs, fentanyl and compounds with similar chemical structures (fentanyl analogues) may be subject to non-medical use (misuse). This may involve the diversion of licensed medicinal fentanyl or fentanyl analogues, or the use of illicitly manufactured material. These very potent compounds have already been implicated in large numbers of deaths amongst drug users in the United States (US) and Canada. There is an ongoing risk of illicit fentanyls increasingly infiltrating the illicit opioid market in the UK, with consequent increases in drug-related deaths that could be substantial.

Note: There is inconsistent spelling used in the medical literature, with use of both 'fentanyl' and 'fentanil'. In this report we have used the International Non-proprietary Names (INN) for those that are licensed human or veterinary medicines (fentanyl, alfentanil, remifentanil, sufentanil, carfentanil) and 'fentanyl' for all unlicensed analogues.

1.2. The public health risk associated with the misuse of fentanyl and its analogues relates to the high potency of these substances. Compared to morphine, the amount of fentanyl required to produce the same pain killing (analgesic) effects is 50-100 times lower. Because of this, users face a high risk of accidental overdose leading to potentially fatal respiratory depression. As with other groups of synthetic psychoactive drugs, a wide range of structural fentanyl variants is possible; most of these have potencies intermediate between fentanyl and morphine but a few (such as carfentanil) are substantially more potent than fentanyl and therefore present a particularly high risk of fatal overdose.

1.3. In July 2017, the then Home Secretary stated in a commissioning letter to the ACMD:

"I am concerned about recent evidence, from drug user deaths and police seizures in the UK, of potent synthetic opioids (fentanyls, including carfentanil) having been added to illicit heroin in the supply chain. Public Health England (PHE) is working with others to gather and assess data on the spread and impact of fentanyls, which will inform the development of appropriate responses. As this work progresses, I may commission the ACMD to provide further advice on this matter. In the interim, it would be helpful if ACMD could, based on a review of the scientific literature on the psychopharmacology of the fentanyls, advise me on the number and nature of known analogues, and their known and likely risk factors..."

1.4. In response to this commission, the ACMD Novel Psychoactive Substances (NPS) Committee have produced this report with the aim to inform the Government on the pharmacology and toxic effects of fentanyl and its analogues and their misuse and the associated harms as documented internationally and in the UK. The report has been written by the ACMD NPS

Committee, chaired by Professor Simon Gibbons until January 2019 and Professor Simon Thomas thereafter.

- 1.5. The recommendations provided aim to improve public health surveillance and minimise the potentially severe health impacts of this potent and hazardous group of substances in the UK.
- 1.6. UK legislation includes a long-standing generic control on fentanyl variants, which classifies almost all those currently being encountered internationally as Class A drugs. Although the legislation remains robust, additional controls on fentanyl precursors are recommended, together with other measures to improve the detection and surveillance of fentanyl involvement in episodes of drug-related toxicity and to reduce the risks of diversion of pharmaceutical fentanyls and the importation of illicitly manufactured fentanyls.

2. Background and Pharmacology

- 2.1. The opium poppy contains several alkaloid compounds ('opiates'), the most important of which is morphine. These produce pain-relief (analgesia), sedation and euphoria by mimicking naturally occurring chemicals within the human body called endorphins, a contraction of 'endogenous morphines'. These chemicals and their synthetic or semi-synthetic analogues ('opioids') interact with a series of receptors within the brain and nervous system termed mu (μ), delta (δ), and kappa (κ) opioid receptors. The pharmacology of opioid receptors is complex, but the μ opioid receptor is particularly important because it is the principle mediator of the analgesia, respiratory depression, euphoria and dependency associated with morphine and other opioids [Gill *et al.*, 2019]. A wide range of drugs have been identified or synthesised that stimulate this receptor (' μ opioid receptor agonists'); these all produce analgesia and euphoria, but they also carry the risk of dependence and potentially fatal overdose.
- 2.2. The characteristic features of opioid overdose are reduced level of consciousness, pinpoint pupils and respiratory depression associated with loss of respiratory reflexes and risk of aspiration. These may rapidly lead to respiratory arrest and death in the absence of appropriate medical treatment. Those at particular risk of death are those who inject opioids or use them in combination with other sedatives (such as benzodiazepines), and those with underlying health conditions [WHO, 2018]. After regular use of opioids, the phenomenon of tolerance develops [Cahill *et al.*, 2016], meaning that regular users need higher doses to obtain the same effect and can tolerate higher doses without developing features of overdose. If use is interrupted for a period of a few days or longer, e.g. during incarceration, this increased tolerance is lost; the user is then susceptible to potentially fatal respiratory depression after exposure to doses that were previously used without complications [WHO, 2018].

2.3. Opioid overdose can be treated by the antidote naloxone, which acts as a competitive antagonist ('blocker') at the μ opioid receptor. This reverses the features of opioid toxicity, improving the level of consciousness and respiratory rate. Naloxone is very effective provided it can be administered in adequate doses before irreversible effects occur, such as brain damage resulting from lack of oxygen delivery.

3. Semi-synthetic and synthetic opioids

- 3.1. Initially, further 'semi-synthetic' medicinal opioids were developed by chemical modification of naturally occurring opiates present in opium. Examples are diamorphine (diacetylmorphine, heroin), codeine, oxycodone, hydrocodone and etorphine. The structural complexity of these drugs makes it commercially unfeasible to synthesise them completely from simple chemicals, so they require manufacture from plant-derived opiates. Chemical modifications profoundly affect pharmacological properties; at the extreme, etorphine, an active ingredient of 'Immobilon', used in projectile darts to anaesthetise large animals [VMD, 2010], has a potency that is over 1,000 times greater than that of morphine [Blane *et al.*, 1967].
- 3.2. Continuing pharmaceutical research that developed understanding of how compounds interact with brain receptors, particularly the μ opioid receptor, resulted in the development of a much broader range of drugs which could produce similar analgesic effects to morphine. Many of these have simpler chemical structures than the morphine-related compounds, allowing synthesis directly from simple precursor chemicals without the need to start from a natural product. These are referred to as 'synthetic' opioids.
- 3.3. As well as providing useful analgesic effects, semi-synthetic and synthetic opioids also produce the euphoria and habituation associated with traditional opiates and are therefore prone to non-medical use. They can also produce potentially fatal dose-related respiratory depression. In the case of the more potent of these compounds, such as the fentanyls, this risk is high. As a result, many synthetic opioids are controlled internationally under the United Nations (UN) Conventions, as detailed later in this report.
- 3.4. In the 1930s, pethidine (meperidine, ethyl-[1-methyl-4-phenylpiperidine]-4-carboxylate), a 4-phenylpiperidine compound originally intended for use as an anti-cholinergic drug, was serendipitously discovered to have an analgesic potency approximately 20% of that of morphine. Pethidine was used widely in the UK for short-term pain relief, e.g. during labour, although medicinal use is now less common.
- 3.5. In the 1960s, the Janssen Pharmaceuticals research team recognised an underlying structural similarity between morphine and pethidine and began a programme to explore related structures. This resulted firstly in the discovery

of phenopiperidine, a μ -opioid receptor agonist twenty times more potent than morphine, and then fentanyl, a 4-anilidopiperidine which has a potency approximately 50 to 100 times greater than that of morphine. This is not as a result of an increased binding affinity at the μ -opioid receptor as for fentanyl this is similar to that of morphine, although some fentanyl analogues (e.g. sufentanil) have more potent binding [Volpe *et al.*, 2011]. Instead, the increased potency of fentanyl results from its high lipid solubility, which allows rapid passage through the blood-brain barrier to achieve high concentrations at its site of action in the brain [Trivedi *et al.*, 2007]. Fentanyls were developed with the intention of producing a safer class of drugs where the doses required to produce analgesia were a much lower proportion of those needed to produce respiratory depression or death, reducing the risk of inadvertent overdose. The potency of some of these compounds, compared to morphine, has been shown to be higher for therapeutic effects than for toxic effects in studies involving rats and mice [Van Bever *et al.*, 1976; Higashikawa & Suzuki, 2008]. These data, however, come from animal studies and their relevance to humans is uncertain.

3.6. The fentanyl molecule is amenable to a wide range of structural modifications to produce chemically-related compounds ('fentanyl analogues'). Extensive exploration of chemical structure-activity relationships has led to several of these analogues being marketed as pharmaceuticals, each with different characteristics, making them suitable for medical or veterinary applications.

4. Pharmaceutical fentanyls

4.1. The fentanyl analogues currently licensed as medicines for human use in the UK are fentanyl, alfentanil, remifentanil and sufentanil. These are all potent drugs with target effects on the brain to relieve pain, but they also have euphoric effects and most have the potential for misuse. Pharmaceutical fentanyls are in everyday hospital use, especially in intensive care units and operating theatres, for anaesthesia and post-operative pain control. They are also used to provide sedation and pain relief for medical procedures such as fracture manipulation. Some are also used by pre-hospital teams, emergency departments, and in primary care, for example, by patients receiving palliative care at home.

4.2. Some fentanyls are not licensed for human use but may be used in veterinary practice. Carfentanil, for example, has been used to sedate large animals. Some important properties of medicinal fentanyls are compared with those of morphine in Table 1 below.

Table 1: Pharmacological properties of medicinal fentanyls compared with morphine

Drug	Therapeutic potency compared to morphine	Routes available	Half-life (intravenous)	Notes
Morphine	1 (reference compound)	Parenteral, oral	120-240 mins	Shown for comparison
Fentanyl	50-100	Parenteral, oral, buccal (tablets, lollipops), skin (patches), basal (spray)	141-853 mins	Action prolonged after high doses
Alfentanil	30	Parenteral, buccal/nasal spray	90 mins	Rapid onset of action
Sufentanil	500	Sublingual	164 mins	Rarely used in the UK
Remifentanil	100-200	Parenteral	3-10 mins	Very short half-life. Used by continuous infusion

Notes:

Therapeutic potency: Numbers greater than 1 indicate higher potency than morphine

Half-life: Time taken for the plasma concentration to fall by half due to elimination

4.3. Fentanyl

- Fentanyl itself is a potent and fast-acting μ opioid receptor agonist, with a relatively short duration of action, in part because of redistribution from the brain to other tissues. It has a high therapeutic index i.e. the ratio of the dose needed to produce toxicity to that required for the analgesic effect is higher than for morphine. These properties make fentanyl attractive for clinical use.
- Fentanyl is metabolised extensively by the liver and there is substantial 'first pass' hepatic metabolism. This means that, after ingestion, most of the drug is removed as it passes from the gut through the liver and before it can reach the systemic bloodstream. This route is therefore much less effective than direct delivery of fentanyl into the bloodstream by injection. The transdermal, buccal and nasal routes, however, are useful as these avoid hepatic first pass metabolism.
- Fentanyl was initially marketed in 1963 as an intravenous anaesthetic ('Sublimaze') and has become widely used for this purpose in operating theatres. Subsequently, other presentations have been developed for different routes of administration. Fentanyl patches (e.g. 'Duragesic') were designed to provide a steady release of the active ingredient for longer term pain relief. The patch is constructed with a reservoir of material and a permeable membrane which is held in contact with the skin. The active ingredient is formulated in a carrier gel so that it can pass from the reservoir through the membrane and the skin to enter the bloodstream at a near constant rate. Patches are designed to be worn for extended periods - typically three days - during which time a relatively constant dosage is absorbed each day. The

patch is then discarded, folding the sticky sides together, before a fresh one is applied.

- Buccal absorption tablets and films, nasal sprays and 'lollipops' (a lozenge mounted on a stick, e.g. 'Actiq®') have also been developed to provide rapid alleviation of pain following absorption of fentanyl through the oral or nasal membranes. In 2017 the UK's armed forces adopted fentanyl 'lollipops' as a replacement for morphine for immediate battlefield pain relief.

4.4. Alfentanil

- Alfentanil is a rapid onset and short-acting drug because it is highly lipid soluble and redistributes rapidly to other tissues and away from the brain. It can be used to facilitate emergency anaesthesia, to maintain sedation and analgesia in the intensive care setting. It is also administered by infusion in palliative care. Its potency is about one third of that of fentanyl. A spray formulation for buccal or nasal application is also available but infrequently prescribed in the UK.

4.5. Sufentanil

- Sufentanil is a highly potent opioid - 5-10 times more potent than fentanyl - currently licensed as a sub-lingual tablet for acute, moderate-to-severe, post-operative pain relief. Use in the UK is currently very uncommon.

4.6. Remifentanil

- Remifentanil is an opioid drug with approximately double the potency of fentanyl. It is administered as an infusion during anaesthesia for pain control. It has a particularly short half-life and duration of action because it is rapidly broken down by enzymes (esterases) in the blood and tissues. As a result, once the infusion is stopped, its effects dissipate over a few minutes, resulting in rapid recovery. This very short duration of action makes remifentanil unattractive for non-medical use.

4.7. Carfentanil

- Carfentanil has a therapeutic potency more than 100 times greater than fentanyl, although its relative potency for producing toxic effects may not be as great as this [Van Bever *et al.*, 1976]. Although too potent for safe use in humans, it has been used in veterinary practice. It was the active ingredient of 'Wildnil', used in dart-gun projectiles to sedate large animals [WHO, 2017]. There is a significant risk of death to anyone handling the drug without facilities designed for handling such toxic substances, but there is a case report of an accidental exposure to the eye from a broken ampoule successfully treated with naloxone. Advice on preventing occupational exposure of first responders has been issued in the US [Moss *et al.*, 2017]. The carfentanil analogue lofentanil (3-methyl carfentanil) is even more potent and longer-acting than carfentanil and is only used for research.

5. Clinical effects

- 5.1. All the fentanyl class drugs exhibit a rapid-onset of pain relief when administered via injection or via the buccal or nasal routes. They are associated with a feeling of warmth, relaxation and euphoria. As anticipated from their pharmacology, these effects may be more intense but last a shorter time than those of morphine and diamorphine [Amlani *et al.* 2015; Ciccarone *et al.*, 2017; Macmadu *et al.*, 2017].
- 5.2. Fentanyls produce the same dose-related adverse effects as other opioids; itchy skin, constipation and delirium are common. The most dangerous adverse effect is respiratory depression, when the rate of respiration is initially reduced, followed by a reduction in breath volume (and subsequent large 'sighing' breaths) with increasing opioid doses. As for other opioids, respiratory arrest is a pre-terminal feature in fentanyl overdose. The lipid solubility of fentanyl allows fast penetration into the brain and rapid therapeutic effects, but it also means that respiratory depression may occur more quickly after overdose than with heroin. This reduces the window of opportunity for effective treatment with naloxone [Gill *et al.*, 2019]. Intravenous administration of fentanyls may also produce fentanyl-induced respiratory muscle rigidity (FIRMR), which can cause increased stiffness of the chest wall ('wooden chest') and laryngospasm (vocal cord closure), further restricting breathing. This effect of fentanyls is distinct from the respiratory depression caused by opioids and can occur rapidly after intravenous fentanyl use and occasionally after modest doses [Streisland *et al.*, 1993; Vankova *et al.*, 1996; Mayer *et al.*, 2018; Kinshella *et al.*, 2018; Torralva & Janowsky, 2019].
- 5.3. Inadvertent overdose of fentanyl and its analogues through medical or non-medical use can be reversed by the competitive μ opioid receptor antagonist, naloxone. The dose required in an emergency is dependent upon many factors, however. The current community provision of naloxone kits for the treatment of suspect overdoses will assist in the management of fentanyl overdose. Some patients with fentanyl overdose have required relatively high doses of naloxone, sometimes up to 2.4 mg [Mayer *et al.*, 2018]. Current recommended naloxone dosing in the UK for acute treatment of adults with heroin overdose by healthcare professionals is to administer an initial injection of 0.4 mg. If this is ineffective, a further injection of 0.8 mg should be administered after 1 minute; this can be repeated after another minute if needed (total dose 2.0 mg). If that is ineffective, a further dose of 2.0 mg is advised. [NPIS, TOXBASE, www.toxbase.org] This regimen allows the administration of up to 4 mg naloxone within 3 minutes for those patients who need a high dose. This is an appropriate and flexible strategy which balances the risk of delayed reversal of respiratory depression with that of causing acute withdrawal from excessive naloxone use. This rapid dose titration is also appropriate for those exposed to highly potent analogues such as carfentanil [Lynn and Galinkin, 2018]. Naloxone, however, is not effective for

treating FIRMR or laryngospasm provoked by fentanyl. For such patients, use of a muscle relaxant, endotracheal intubation and mechanical ventilation are required.

- 5.4. Pre-provision of naloxone to heroin users ('take home naloxone', THN) is effective at preventing heroin-related deaths, including those where heroin may have been fortified by fentanyl or a fentanyl analogue. Prenoxad® pre-filled syringes contain 2.0 mg naloxone in 2 ml solution for intramuscular injection. In the community an initial dose of 0.4 ml (0.4 mg) is advised, but this can be repeated every 2-3 minutes until an adequate response is obtained or the whole syringe has been administered [Electronic Medicines Compendium (EMC), 2019c]. This regimen is likely to be effective for the majority of cases of fentanyl toxicity, however, the total dose may be too low, and the rate of administration too slow for the most severe cases. Naloxone nasal spray (Nyxoid®) is also available with a recommended dose of 1.8 mg that can be repeated if needed. Peak blood concentrations occur about 15 minutes after dosing (although effects will be evident before that) and although less than half of the naloxone reaches the bloodstream (systemic bioavailability 47%) [EMC, 2019b] this preparation would also be useful in all but the most severe cases of fentanyl toxicity, or those complicated by FIRMR or laryngospasm.
- 5.5. While licensed THN preparations may not be ideal for the most severe cases of fentanyl toxicity, the largest risk relates to lack of availability. It remains important to encourage dispensing of THN kits to those at risk and to provide appropriate training, as recent evidence demonstrates limited coverage. In England, where Local Authorities are responsible for dispensing, estimated coverage of THN among opiate clients in community drug treatment was 11 per cent in 2017/18 [Carre, 2019]. PHE provided advice on widening availability in July 2017 [PHE, 2017]. In Scotland it was estimated that 37.6% of at-risk individuals had received THN kits [ISD 2018].

6. Non-medical use of pharmaceutical fentanyl

- 6.1. The ACMD has previously provided advice on the diversion and illicit supply of medicines, including some information on fentanyl [ACMD, 2016b], which has high abuse potential and is attractive to some opioid users [Sellers *et al.*, 2006; Morales *et al.*, 2019]. Addiction to fentanyl has been clearly documented, comprising of both physical withdrawal states and a psychological need for the drug.
- 6.2. While pharmaceutical fentanyl were only available as injectable anaesthetics, potential non-medical use was limited to those who had access to material through their work (e.g. healthcare professionals), or by theft from pharmacies [Bryson & Silverstein, 2008]. However, since skin patches entered clinical use, methods for misuse of these formulations have been developed. Used patches still contain a significant amount of fentanyl, 28-

84% of the original content or up to 8.4 mg for a 10 mg patch [Marquardt *et al.*, 1995]. There is therefore a risk for misappropriation and misuse, especially as recommended therapeutic fentanyl doses for adults breathing spontaneously are 0.2 mg or lower [EMC., 2019a]. Misuse of patches may involve cutting up the reservoir for smoking, chewing, swallowing or rectal insertion, extracting the active material for injection or nasal insufflation ('snorting') or heating the patch (e.g. on foil or in a glass chamber) and inhaling the fentanyl emitted [Lucyk & Nelson, 2016]. The unmeasured nature of such techniques means that the overdose risk is substantial, and there have been low but persistent numbers of fentanyl-related overdose deaths in the UK over many years (detailed below). Safe disposal advice is provided with the patches, but these warnings are concerned with avoiding the risk of accidental exposure, rather than prevention of diversion. In North America, where non-medical fentanyl use has become a major problem, efforts have been made to reduce the risk of non-medical use of fentanyl patches. For example, Ontario deployed a "one in, one out" strategy, where prescribers require pharmacies to ensure that patients return used patches when collecting fresh supplies. However, so great is the incentive to access material, 'fake' patches have been presented to pharmacies in order to obtain fresh material. [CBC, 2017]

- 6.3. A study from the Australian Institute of Criminology in March 2019 [Ball, 2019] analysed fentanyl listings on six darknet markets and found that just over 40% of fentanyl listings related to fentanyl patches, over 26% related to powders and over 24% related to tablets. The rest of the forms included solutions, sprays, and unknown. In total, the authors estimated that 15-22kg of fentanyl was available from 102 vendors on any given day, but they believed this to be an underestimate.
- 6.4. Misuse of other pharmaceutical fentanyls, such as buccal tablets or lollipops, can occur but is infrequently reported in the UK, related perhaps to low rates of primary care prescribing. Current UK prescribing data indicates that the bulk of fentanyl prescribing in primary care is in the form of patches - but prescribing of patches has been declining since 2016. Prescribing is stable or declining for all other fentanyl products and fentanyl analogues with the exception of alfentanil, where increases are likely to reflect increasing use for palliative care at home (Annex 1).
- 6.5. The National Poisons Information Service (NPIS) is commissioned by PHE to provide information and clinical advice to UK health professionals managing patients who may have been exposed to potentially toxic substances, including drugs of misuse. For most cases, information is provided via an internet database called TOXBASE®, but a 24/7 telephone enquiry line is available with consultant support for more complex cases or when TOXBASE cannot be accessed. The number of accesses to TOXBASE® and NPIS telephone enquiries reflect (but do not measure directly) the frequency of

contacts between health professionals and patients presenting following suspected exposures. Five-year NPIS data for fentanyl, fentanyl analogues and other new synthetic opioids (NSOs) are provided in Annex 2, together with data for heroin for comparison. Telephone enquiry data include overall enquiry numbers (excluding enquiries about therapeutic use) and enquiries where the exposure was classified as 'recreational'. Fentanyl-related telephone enquiries are uncommon; most of those that are made relate to therapeutic use of patches, with the highest numbers of enquiries received in 2015 with reductions since. A small minority of these were classified as recreational misuse.

6.6. Pain control is an important aspect of health care, but there is a lack of high-quality published information on diversion and illicit supply of strong opioid drugs, including licensed fentanyl. Information currently available does not suggest increases in fentanyl diversion, but manufacturers of strong opioids, drug regulators and funders of research should be encouraged to address this evidence gap.

7. Illicitly manufactured synthetic opioids

7.1. Manufacture and distribution of synthetic opioids presents a potentially lucrative opportunity for criminals because small and easily concealed amounts can produce euphoric effects similar to those produced by much larger amounts of traditional plant-derived opiates, such as morphine and heroin. Synthetic opioids may be sold overtly to users, as some may prefer to use a high purity high potency compound and different routes of administration may be available (e.g. snorting, vaping). Illicit fentanyls can also be used to fortify a heroin product to increase its potency. The mixture may then be sold to users as heroin, without them being aware that it includes a synthetic opioid. Because of the potency of fentanyls and other synthetic opioids, there is a high risk of overdose with both these scenarios. Fentanyl and its analogues may also be found in counterfeit medicines or may contaminate other illicit drug products.

7.2. The synthetic chemistry expertise required to produce synthetic opioids and the risk to the chemist involved has previously meant that most opioids reaching the illicit market had been diverted pharmaceutical compounds. However, over the last fifty years, there have been occasional outbreaks in the US and elsewhere when skilled 'underground' chemists have been able to produce materials and introduce them into the illicit market [Ayres *et al.*, 1981; Fernando 1991; Boddiger 2006]. Until recently, these outbreaks were episodic and localised and were usually made evident by an associated cluster of fatalities. Once alerted, law enforcement was usually able to trace the supply back to its source and intervene to prevent further production.

7.3. Since 2013, there has been a substantial increase in the international availability of illicitly produced synthetic opioids, including fentanyls. These

have primarily been sourced from China [USCC 2018], using a combination of a well-skilled pharmaceutical industry, internet-enabled international communication and payment systems, and the rapid international transport systems for parcels developed to service internet commerce. China has taken several measures to address the production and distribution of synthetic opioids. Mexico has long been a route via which opiates are smuggled into the US, but there are now reports that fentanyl production for the North American market is now becoming established in Mexico [CFR 2019]. In principle, any jurisdiction with a competent pharmaceutical production infrastructure has the potential to become a source of supply.

- 7.4. Illicitly produced fentanyl analogues have become the most widely-encountered and harmful NSOs reaching the illicit market but non-fentanyl NSO compounds such as MT-45, AH-7921 (both slightly less potent than morphine) and the closely-related U-47,700 (around five times more potent than morphine) have also been encountered. Each of these has been controlled in the UK under the Misuse of Drugs Act as named Class A drugs.

8. Illicit fentanyl analogues

- 8.1. The chemical structure of fentanyl can be modified in a variety of ways to produce compounds with different characteristics, including speed of onset, duration of effect, and potency. At the extreme, substances such as carfentanil and the longer-acting lofentanil have analgesic potencies approximately 10,000 times greater than morphine. Their relatively low production cost and high potency makes them highly lucrative materials if illicit suppliers can use them to replace or supplement traditional opiates such as heroin. Small quantities are easy to conceal for transport locally (e.g. into prisons) or internationally, before extensive dilution by local distributors to produce many individual doses and the opportunity for substantial profits.
- 8.2. Until recently, the multi-stage synthetic process, the exposure risks associated with handling the pure materials, the requirement for an effective distribution network and the risks to end-users of overdose had limited the impact of these materials on the drug market.
- 8.3. Illicit fentanyls may be presented in powder form, either pure or diluted with cutting agents such as paracetamol and caffeine ('bash') or mixed into heroin to fortify the product. In the US, fentanyls have had their greatest impact in those areas where heroin is circulated in powder form, as it is much more difficult to mix fentanyls into the 'black tar' form of heroin that makes up about half of the heroin originating from Mexico [DEA, 2018a]. Fentanyls have also appeared as components of illicitly produced tablets, often deliberately manufactured to resemble legitimate pharmaceuticals, or as solutions intended for use as nasal sprays which permit metering of dosage. Preparations suitable for vaping have also been encountered [Rogers *et al.*, 2016; Rojkiewicz *et al.*, 2017].

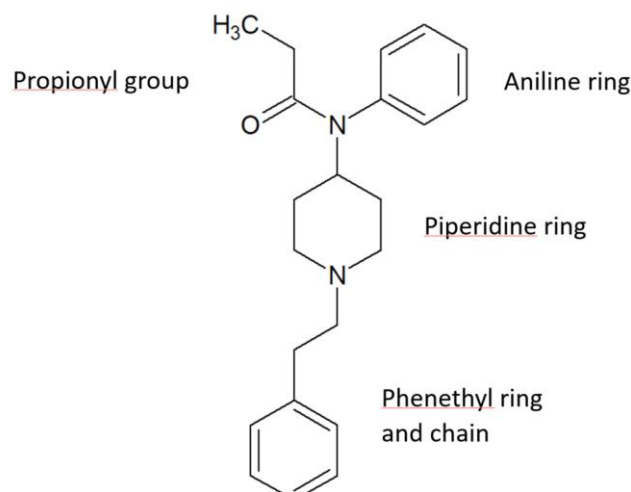
8.4. The potency of the materials means that the risk of accidental overdose causing death through respiratory depression is very high. Careful dilution before administration is required, something which cannot be relied on within illicit distribution channels.

8.5. In North America, where there was already a large community of habituated opioid users, the large-scale introduction of illicit fentanyl has significantly infiltrated the heroin market. In the US, opiate and opioid-related deaths have risen rapidly. Much of this increase is associated with the entry of fentanyl into the illicit opiates market. Canada has also experienced rapidly increasing levels of overdose fatalities, particularly in the western provinces of British Columbia and Alberta. More recently, there has been increasing evidence from law-enforcement agencies of fentanyl entering European drug markets, including the United Kingdom. These trends are described in more detail below.

8.6. Production of fentanyl and analogues

- Janssen's original synthetic route to produce fentanyl was patented in the 1960s; since then, several other synthetic routes have been developed to reduce cost and improve yields. These have been published in patents and scientific journals, are easily accessible via the internet and have also been circulated in 'underground' drug discussion groups. Probably the most well-known alternative synthetic route is the 'Siegfried method', originally described in the 1980s and subsequently improved by other chemists [Synthesis of Fentanyl, 2015]. This is a four-step process which starts from piperidone to produce *N*-phenethylpiperidone (NPP) and then 4-anilo-*N*-phenethylpiperidine (ANPP) before a final room temperature conversion to fentanyl by reaction with propionyl chloride. The circulated method included suggestions on how other variants of fentanyl can be produced. The author also warned of the dangerously high potency of the product and of its highly addictive nature.

Figure 1: Chemical structure of fentanyl



- Each of the four parts of the fentanyl structure (Figure 1), the aniline ring, the piperidine ring, the phenethyl ring and chain and the propionyl group - can be modified to produce variants with retained, and in some cases enhanced, potency. When combinations of such modifications are included, many hundreds of potentially active variants are possible. Some have been characterised as potential pharmaceuticals, with synthetic routes and performance characteristics published in the open scientific literature. Chemists wishing to manufacture and sell illicit drugs have utilised this structural flexibility either to produce particularly potent or long-lasting variants, or to develop 'designer' versions intended to circumvent legal controls that address specifically named variants.
- The recent surge in fentanyl variants reaching the illicit drug market has been centred around the simplest type of these variants, where the propionyl chloride, which is reacted with ANPP in the final step of the 'Siegfried method', is replaced with another acid chloride. For example, use of acetyl chloride results in replacement of the 3-carbon propionyl group by a 2-carbon acetyl group to yield acetyl fentanyl, one of the first of the fentanyl analogues to be encountered in the recent surge in fentanyl abuse. Although less potent than fentanyl, acetyl fentanyl is approximately twenty times more potent than morphine and rapidly led to fatalities when it entered the illicit opiate market in the US [Lozier *et al.*, 2015].
- This approach to fentanyl variant production was especially attractive as, until October 2017 [INCB, 2017], the immediate precursor to these types of variants, ANPP, was uncontrolled in most countries and commercially available at low cost. This precursor required only the addition of the appropriate acid chloride to produce the desired variant. As of January 2018, ANPP is listed under category 1 of the precursor chemical licensing register (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/779992/PC_Wallchart_domestic_February_2019_V6.pdf).

Note: Category 1 covers the most sensitive substances (the 'main' drug precursors).

- In addition to potency, the prolonged duration of effect of some of the variants is of significance as naloxone, the first-line antidote for fentanyl overdose, has a relatively short half-life. Initially effective treatment may be followed by a relapse, especially if a longer-acting fentanyl has been used. This necessitates longer medical observation.

8.7. Economics of illicit production and distribution of fentanyl

- Illicit synthesis and distribution of fentanyls presents a significant opportunity for profit. In very broad terms, one gram of fentanyl is equivalent in value to around twenty grams of pure diamorphine (heroin), or about fifty grams of 'street' heroin (assuming a purity level of street heroin of about 40%). The

production cost of a kilogram of fentanyl has been estimated at 5,000 US Dollars (USD), but the potential distribution value (when diluted to the equivalent of 50 kg of synthetic 'street' heroin) is around 5 million USD. Extrapolating these economics to the much more potent carfentanil increases the potential profitability even more. Further advantages are that the synthesis and distribution of synthetic opioids avoids the need for poppy growing, opium harvesting, morphine extraction, conversion to heroin and international smuggling of bulky consignments; each stage of which represents both a business risk and a cost. There is therefore a significant financial incentive for criminals to obtain and distribute potent synthetic opioids such as the fentanyls. Cowan (1986) proposed an "Iron Law of Prohibition" suggesting that illicit versions of prohibited materials will tend towards the most potent forms.

9. Synthetic opioids in North America

- 9.1. Over the last two decades there has been large scale commercial marketing to physicians and the general public of potent pharmaceutical opioids such as oxycodone as a low risk route to pain relief across North America. As a result, the US, with 5% of the world's population, now accounts for around 80% of the world's consumption of opioids, with 17% of adults in the US receiving one or more prescriptions for opioids in 2017 [CDC 2018]. This widespread use has given rise to a large community of habituated users, estimated to be more than two million individuals. Once established, this demand was serviced by large-scale diversion and over-prescription of pharmaceutical opioids, including the operation of 'pill mills', commercial operations providing opioids by remote prescription.
- 9.2. As the nature and scale of what had become known as 'the prescription opioid crisis' (Phase 1 of the opioid epidemic) had been realised, steps were taken to reduce prescribing levels and to close down the 'pill mills'. As habituated users encountered increasing difficulties accessing pharmaceutical opioids, they sought alternative sources of supply - including the illicit heroin market (Phase 2). In one study, heroin use incidence was 19 times higher among those Americans who reported prior non-medical analgesic use and 80% of new heroin users had a history of such use [Muhuri *et al.*, 2013]. This large user-base provided a ready market when illicit synthetic opioids were introduced (Phase 3) either as ingredients of counterfeit pharmaceutical products or as replacements for or extenders of powdered heroin. As a result, the infiltration of illicit synthetic opioids into the North American heroin and diverted pharmaceutical opioid markets has increased rapidly.
- 9.3. Fentanyls have also been found as additions to other types of illicit drugs, including stimulants such as cocaine [DEA, 2018b] and methamphetamine [Tupper *et al.*, 2018]. This could represent accidental contamination associated with use of common equipment, or deliberate addition to

encourage opioid dependency. Unexpected exposure to stimulant users, without previous use of or tolerance to potent opioid drugs, presents a particular hazard. As an example, fentanyls have been identified increasingly in cocaine overdose deaths in New York [Nolan *et al.* 2019].

9.4. As fentanyl variants have become controlled at the international and national level (see below), novel variants have rapidly appeared as replacements for the banned materials, as seen with other types of NPS, such as synthetic cannabinoids.

9.5. In the US, the death toll from drug overdoses exceeded 70,000 during 2017, three times higher than in 2000 and 10% higher than in 2016. To put this in context, this is higher than the annual death toll from road traffic collisions (approximately 40,000) [NSC, 2019] or the total number of American service personnel killed throughout the Vietnam War. Of these drug overdose deaths, 47,600 were opioid-related. Within the opioid-related death figure, 15,482 are ascribed to heroin and 28,466 to synthetic narcotics other than methadone, (a category dominated by fentanyls). Of the heroin deaths, 8,091 were recorded as involving other synthetic narcotics. In 2018 deaths related to synthetic narcotics other than methadone had increased 9-fold since 2013 and 35-fold since 2000 (Table 2). Deaths per 100,000 population have increased from 0.3 in 1999 to 1.0 in 2013, 1.8 in 2014, 3.1 in 2015, 6.2 in 2016, and 9.0 in 2017, with the latter figure incorporating rates of 13.0 per 100,000 in males and 5.0 in females, with 11.8-fold and 5.6-fold increases since 2013 in males and females respectively [National Institute on Drug Abuse (NIDA), 2019]. In October 2017 the US President declared the level of opiate-related overdose deaths to be a National Public Health Emergency and proposed a 13 billion USD budget over two years to address the issue.

Table 2: Drug overdose deaths in the United States involving selected prescription and illicit drugs. National Institute on Drug Abuse data. 2013-2017 shown with data for 2000

	2000	2013	2014	2015	2016	2017
All deaths	17,415	43,982	47,055	52,404	63,632	70,237
Any opioid	8,407	25,050	28,647	33,091	42,249	47,600
Heroin	1,842	8,257	10,574	12,989	15,469	15,482
Other synthetic narcotics (other than methadone)	782	3,105	5,544	9,580	19,413	28,466

Note: For other synthetic narcotics: This category is dominated by fentanyl-related overdoses

9.6. The problem of illicit fentanyl and its analogues in North America is not confined to the US. In Canada, there has also been high volume prescribing of potent opioids, with one in five Canadians using a medicinal opioid during the so called 'peak years' (2008-2010). An unintended consequence of subsequent efforts to restrict opioid prescribing, including by issuing restrictive prescribing guidelines and intensive prescription monitoring, was the establishment of a population of habituated opioid users no longer

receiving prescriptions. This generated increasing demand for illicit opioids [Fischer *et al.*, 2018; Belzak and Halverson, 2018].

9.7. There were 4,460 opioid-related deaths reported in Canada in 2018 (12 deaths per 100,000 population), 72% of which involved males and 70% of which involved a fentanyl. This figure represents a sharp increase since 2016, when there were 3017 opioid-related deaths with 50% involving a fentanyl. Fentanyl-related deaths have been most frequent in British Columbia, Alberta and Ontario [Government of Canada, 2019a]. Recent data from Vancouver, British Columbia, indicates that more than 90% of samples bought as heroin tested positive for fentanyl [Tupper *et al.*, 2018], and there are strong correlations between numbers of seized fentanyl samples and total overdose deaths [Baldwin *et al.*, 2018].

10. North American initiatives in response to synthetic opioids

United States

- 10.1. In addition to supportive mechanisms such as dependence treatment services and provision of Naloxone nasal sprays to first responders, friends, and relatives of known opiate users, the US is undertaking a variety of enforcement-related actions to address their synthetic opioid crisis. For example:
- As part of the initiative to reduce the circulation of prescription opioids, the US established an 'Opioid Fraud and Abuse Detection Unit' in 2017, specifically to investigate and prosecute health care fraud and overprescribing involving prescription opioids.
 - A 'Prescription Interdiction and Litigation (PIL) Task Force' was announced in 2018 to oversee all stages of the opioid manufacture and distribution process and prosecute any unlawful practices identified.
 - Sentencing guidelines have been amended so that cases involving known marketing of fentanyl or fentanyl analogue-containing materials attract more severe penalties than those involving traditional opiates [USSC, 2018].
 - At the end of December 2017, the US announced its intention to move to an emergency broad control on all fentanyl variants [DEA, 2017] rather than controlling individually named compounds or relying on the operation of their Federal Analogue Act. The control is similar to the UK's generic control on fentanyls, but differs in some respects (see Annex 5, under 'United States').
 - Postal importations have been identified as a major route for synthetic opioids to enter the US. A number of measures have been adopted to address this problem [HCEC, 2019]:
 1. The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities ('SUPPORT') Act 2018 required additional resources to be made

available to increase inspection capabilities at International Mail Facilities (IMFs) while the ‘Synthetic Trafficking and Overdose Prevention’ (STOP) Act 2018 required incoming international post to be pre-notified. This specified that 100% of postal packages from China and 70% from the rest of world should be provided with advanced electronic data, giving details of source, destination and contents, rising to 100% by the end of 2020. The Universal Postal Union agreed that all international parcels will require advanced electronic data by the start of 2021.

2. The ‘International Narcotic Trafficking Emergency Response by Detecting Incoming Contraband with Technology’ (INTERDICT) Act 2018 provided funding for additional equipment and staff for chemical screening at importation points, especially for mail and fast parcels. This includes X-ray screening units, glove boxes for use in examining suspect materials and provision of naloxone supplies for operators. A major limiting factor within IMFs was found to be ensuring adequate space was available for the teams and their equipment – where necessary, funding is being provided to set up temporary and mobile facilities. Drug detection dogs are now being trained to detect fentanyl concealments.
 3. To further assist in detection at IMFs, a 1.5 million USD challenge fund for new technologies to detect opioids using non-intrusive systems was launched. The winning technology combined a 3D X-ray computed tomography scanner with automated detection algorithms [ONDCP, 2019].
- To combat the ‘darknet’ trade in synthetic opioids, the US established a ‘Joint Criminal Opioid Darknet Enforcement (‘J-CODE’) team in January 2018. This is staffed by Federal Bureau of Investigation (FBI) agents and is intended to disrupt hidden markets by means of investigations and ‘sting’ operations.

Canada

10.2. Canada has also adopted a raft of actions in response to the opioid crisis in that country across five domains, as follows [Government of Canada, 2019b].

- **Increased access to treatment** – by methods including:
 - facilitated methadone prescribing and use of medical heroin;
 - increased opioid agonist therapy in federal correctional facilities;
 - enhanced delivery of culturally appropriate substance use treatment and prevention services in First Nations and Inuit communities;
 - improving access to treatment services through an Emergency Treatment Fund for provinces and territories; and,
 - supporting the development of a national treatment guideline for injectable opioid agonist treatment and funding pilot projects.
- **Increased access to harm reduction** – by methods including:

- approving supervised consumption sites with authorised drug checking services;
 - enabling establishment of overdose prevention sites;
 - providing improved legal protection for individuals who seek emergency help during an overdose;
 - launching a drug checking technology challenge;
 - launching a pilot project to examine needle exchange programs in federal correctional facilities;
 - making it possible for overdose prevention sites to operate in federal correctional facilities;
 - providing enhanced funding through the Substance Use and Addiction Program; and,
 - facilitating access to naloxone, including for remote and isolated First Nations and Inuit communities.
- **Increased awareness and prevention** – by supporting:
 - the development of opioid prescribing guidelines and national treatment guidelines for opioid use disorders,
 - updated opioid product monographs,
 - further restricted opioid marketing activities and provided new resources to enforce existing rules,
 - expanding public awareness around opioids and their harms of and by working with health professionals to decrease stigma and related barriers to care.
- **Decreased tainted drug supply** – by:
 - equipping border agents with tools to intercept fentanyl and other dangerous substances at the border,
 - pursuing scheduling amendments to restrict importation of chemicals used to produce fentanyl and related compounds,
 - implementing a national operational strategy aimed at detecting, disrupting and dismantling criminal networks,
 - working with domestic and international partners to reduce the illegal opioid supply,
 - supporting education and training for law enforcement,
 - supporting law enforcement with drug seizures and dismantlement of illegal drug operations,
 - working with private sector partners to address the laundering of the proceeds of fentanyl trafficking.
- **Increased evidence** – by
 - coordinating national data collection and publishing quarterly reports on apparent opioid-related deaths and harms,
 - releasing alerts on dangerous drugs;
 - monthly data and quarterly reports on drugs submitted for analysis following law enforcement seizures,

- supporting research and knowledge sharing,
- increasing understanding of Canadians' knowledge of the opioid issue; and,
- establishing a Canadian Pain Task Force to assess best and leading practices that could improve the prevention and management of chronic pain in Canada.

11. Synthetic Opioids in Europe

- 11.1. Between 2009 and 2018, 49 new synthetic opioids (NSOs) were reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) EU Early Warning System on new psychoactive substances; 34 of these were fentanyl. The first 8 months of 2019 saw a further 7 NSOs reported, of which 1 was a fentanyl. The EU Early Warning System, operated by the EMCDDA and Europol, received reports from 30 national early warning systems across Europe. The national systems routinely report data, such as seizures of new psychoactive substances from police and customs as well as poisonings, to the EMCDDA.
- 11.2. The EMCDDA reported large increases in the availability of NSOs in parts of Europe during 2016-17. In 2017 NSOs were the largest NPS group reported by the EMCDDA EU Early Warning System on new psychoactive substances, accounting for 13 (25%) of the 51 NPS reported in that year, with 10 of these being fentanyl (Annex 3) [EMCDDA, 2018].
- 11.3. As a percentage of NPS seizures reported by law enforcement agencies in Europe in 2017, NSOs accounted for 1300 (2%) of the 64,160 reported to the EMCDDA EU Early Warning System on new psychoactive substances [EMCDDA, 2019]. Of the 1300 new synthetic opioid seizures reported, 940 (72%) were fentanyl derivatives, presenting as 14.3 kg of powders, 1.9 litres of liquids, 10,551 tablets and 2291 patches. Less commonly other synthetic opioids were involved, such as U-47,700 and U-51754. Most seizures were reported to have originated from China, but there have been occasional reports of production in illicit European laboratories. Since 2016, there has been a small reduction in total numbers of new synthetic opioid seizures reported. Of these reported seizures there has been a drop in the amounts of synthetic opioid-containing liquid seized but increases in the amounts of synthetic opioid-containing powders and tablets seized. Less commonly, fentanyl has been found in blotters and plant material [EMCDDA, 2019].
- 11.4. In early 2018, the EMCDDA reported that examples of 'fake' pharmaceuticals (Xanax and Oxycontin tablets) containing fentanyl, similar to those which had been seen in the US, had been identified in Denmark and Sweden. Unlabelled nasal sprays containing acryloylfentanyl were detected in Sweden in 2016 and nasal sprays containing acryloylfentanyl, furanylfentanyl, 4-fluoroisobutyrylfentanyl, tetrahydrofuranylfentanyl and

carfentanil have also been reported elsewhere in Europe. There have also been reports of e-liquids containing fentanyl for use by vaping [EU EWS 2018a, 2018b; 2018c; EMCDDA 2018].

- 11.5. The EMCDDA reported more than 250 deaths linked to fentanyls in Europe in the reporting year 2016-17 with implicated substances including acetylfentanyl, acryloylfentanyl, furanylfentanyl, 4-fluoroisobutyrylfentanyl (4F-iBF), tetrahydrofuranylfentanyl (THF-F), carfentanil, methoxyacetylfentanyl and cyclopropylfentanyl [EMCDDA, 2018].
- 11.6. For carfentanil, there were more than 300 seizures reported by law enforcement agencies in Europe in 2017, amounting to 4 kg of powder and 250 millilitres of liquids. In approximately 50% of seizures reported to the EMCDDA EU Early Warning System, carfentanil was detected in mixtures with heroin or another opioid. The EMCDDA reported that there were at least 61 deaths in 8 European countries involving carfentanil between November 2016 and April 2017; many of those affected were heroin users [EMCDDA 2018].
- 11.7. In 2017, of those entering drug treatment services in Europe citing opioids as their primary problem drug, only 0.5% cited a fentanyl. There are, however, important variations between countries. For example, fentanyls were the most commonly cited opioid in Estonia [EMCDDA 2019].
- 11.8. The EMCDDA has emphasised the importance of high quality forensic and toxicological data for detecting trends in emerging highly potent drugs of misuse such as fentanyl and its analogues. Without this, there is a risk that the involvement of these drugs in episodes of fatal poisoning will be underestimated. Increased investment in toxicological analysis provides a better understanding of drug trends. For example, in Sweden, comprehensive screening for fentanyls doubled the number of cases of drug-related deaths where a fentanyl was identified [EMCDDA 2019].

12. Synthetic Opioids in the UK

- 12.1. In the United Kingdom, prescribing of pharmaceutical opioids has been at a significantly lower level than in North America. A recent report from PHE, however, estimated that 5.6 million people (12.8% of the population) were dispensed at least one opioid prescription during 2017-18, although opioid prescribing has declined slightly since 2016. There is also substantial long-term opioid prescribing; of 1.98 million people in receipt of a prescription in April 2015, 540,000 (27%) received further continuous prescriptions up to March 2018. Opioid prescription was more common for women and increased with age and with social deprivation [PHE 2019]. Pharmaceutical control systems have ensured that there has been little diversion of pharmaceutical opioids, other than a low - but persistent - level of diversion of fentanyl patches (although prescribing of patches has recently declined, see

above). A number of guidelines are also available to help prescribers use opioids appropriately. Of particular importance is the 'Opioids Aware' resource, produced by the Royal College of Anaesthetists' Faculty of Pain Medicine, in partnership with PHE [RCAFP, 2019]. This emphasises the lack of evidence of benefit of opioid prescribing for chronic pain, the harms associated with long-term use of high morphine-equivalent doses and the need to taper or discontinue therapy which is proving ineffective. This 'Opioids Aware' resource has been supported by the National Institute for Health and Care Excellence (NICE) via its Key therapeutic Topic 21 [NICE, 2017] and NICE is also currently developing the clinical guideline *Chronic pain: assessment and management*, expected to be published in August 2020.

- 12.2. It has been suggested that the risk of fentanyl adulteration of heroin may be lower in the UK than in North America because the UK market favours the base form, (suitable for smoking and injection) as opposed to the salt form (suitable only for injection) which is more common in the US. In addition, the purity of street heroin in Europe is relatively high compared to the US, decreasing the incentive for adulteration [Torjesen 2018]. As yet, there has been no evidence of illicit laboratories producing synthetic opioids within the United Kingdom, and the level of infiltration of synthetic opioids into the established heroin distribution systems has remained low. Since 2017, there have been incidents of small-scale importation, dilution and distribution of illicit synthetic opioids which have led to clusters of deaths. To date, law enforcement has been able to identify and interdict these distribution networks rapidly.
- 12.3. Within the UK, recent examples of fentanyl distribution and associated overdoses and deaths have been episodic, resulting from individuals obtaining and distributing materials via the internet. In 2017, the National Crime Agency (NCA) reported heroin containing fentanyl seized in Yorkshire. There was also a heroin-related death in April 2017 where carfentanil was identified at post mortem. Following targeted testing in the North East of England, samples from further apparent heroin-related deaths were found to contain fentanyls [NCA 2017]. More recently, however, the majority of UK police forces have reported fentanyl-related deaths. Law enforcement authorities have to date been successful in rapidly identifying sources and distribution networks and in intervening to prevent further casualties. Should more established UK heroin distribution groups begin to obtain and include fentanyls within their product, the problem has the potential to become much more intractable.
- 12.4. In December 2018, the Metropolitan Police seized 3,500 counterfeit tablets of 'Percocet' that were found to contain fentanyl only. In spite of the high first pass metabolism of fentanyl, similar fake tablets have been reported to cause deaths in the US [CDC 2017]. Percocet is a combination analgesic

widely used in the US containing the opioid oxycodone together with paracetamol.

12.5. The Welsh Emerging Drugs and Identification of Novel Substances Project (WEDINOS) analyses samples of drug samples submitted anonymously by users from across the UK. Of 5,460 samples submitted and analysed between October 2013 and March 2017, 22 samples were found to contain fentanyl or the analogues ocfentanil, furanylfentanyl, carfentanil, acetylfentanyl or thiofentanyl [WEDINOS 2017]. Betahydroxyfentanyl and cyclopropylfentanyl have also since been detected.

12.6. Drug seizure data for England and Wales is available from Public Health England for the period January 2017 to June 2019. Over that period the fentanyl analogues detected (and the number of seizures they were detected in) were carfentanil (16), cyclopropylfentanil (4), methoxyacetylfentanil (9), benzylfentanil (2), furanylfentanil (2) and furanylbenzylfentanil (1). Fentanyl analogues were detected in 22 seizures in 2017 and 5 seizures in 2018 but have not so far been detected in any seizures made in the first half of 2019. It should be noted, however, there may be delays in sample analyses taking place, so currently available data for 2019 may be incomplete.

12.7. A pilot study screened the urine of 468 adults receiving treatment for opioid use disorder in 14 study sites in England between December 2016 and May 2018. The fentanyl metabolite norfentanyl was detected in the urine of 15 of these (3%); of those, 12 (80%) were unaware of having purchased fentanyl. Over half of the positive samples had other opioids present and the authors estimated that the rate of heroin contamination with fentanyl could have been as high as 6%. These estimates may be conservative as the test methodology used (Alere Drug Screen Test Strip) may not detect evidence of all fentanyl analogues [Bijral *et al.*, 2018].

12.8. NPIS data, including TOXBASE accesses and telephone enquiries, are shown in Annex 2. There was some increase in annual TOXBASE accesses from healthcare professionals relating to fentanyl, carfentanil, alfentanil and remifentanil between 2015 and 2017, but reductions occurred in 2018. For unlicensed fentanyl analogues and other NSOs, accesses have been uncommon but more frequent in 2017 and 2018 than in earlier years. This does not necessarily reflect healthcare professionals seeing more cases; they may have been prompted to look at TOXBASE information in response to increasing education and publicity about fentanyls.

12.9. Fentanyl-related NPIS telephone enquiries are uncommon, with most related to patches (as described above) and other fentanyl related enquiries being uncommon. It should be noted, however, that fentanyl involvement in cases of apparent heroin intoxication cannot be identified without analytical

confirmation and this is not done as part of routine clinical practice. The possibility that some of the heroin-related enquiries to the NPIS involved fentanyl-contaminated heroin cannot be excluded, but there has not been a consistent recent increase in heroin-related enquiries.

12.10. The IONA (Identification Of Novel psychoactive substances) study analysed blood and/or urine samples from 88 adults presenting to participating emergency departments in England, Wales and Scotland with severe drug toxicity following reported non-pharmaceutical opioid use (predominantly heroin) between March 2017 and February 2019. Fentanyl was identified in samples from 3 cases (3.4%) and alfentanil in 2 cases, but in both of those alfentanil had been administered after hospital admission. No other fentanyl analogues or NSOs were detected. There were also 464 study participants presenting with severe toxicity after suspected NPS use; of these 19 (4%) had samples positive for fentanyl, 5 (1%) for alfentanil (therapeutic use documented in 4) and 1 (0.2%) for acetylfentanyl [Dunn *et al.*, 2019].

UK fentanyl-associated deaths

12.11. In England and Wales, a 'fentanyl-associated death' is a death where one or more fentanyls were detected by post-mortem toxicology testing. The data available do not specify if the fentanyl or fentanyl analogue was considered to cause or contribute to the death. Deaths registered as fentanyl-associated in England and Wales increased to 75 in 2017 and fell slightly to 74 in 2018 (Table 3) [ONS 2019]. Carfentanil had not previously been mentioned on death certificates but accounted for 27 fentanyl-related deaths in 2017 [ONS 2018].

12.12. In Scotland, there were 1,187 drug-related deaths in 2018, including 1,021 where an opioid was implicated or potentially contributed to death. Of these, 12 involved fentanyl and in all these cases this was a prescribed preparation [NRS 2019].

12.13. In Northern Ireland, there have been 63 fentanyl-related deaths since 2008 and 3 deaths related to fentanyl analogues. In 2017, fentanyl was mentioned on the death certificate in 13 of 86 opioid-related deaths [NISRA 2019].

12.14. It is inevitable that some deaths involving fentanyl-contaminated heroin are not recognised because specific fentanyl analysis is not done in all apparent heroin-related deaths. Deaths involving heroin and morphine have been increasing recently in England and Wales, Scotland and Northern Ireland.

Table 3. Drug related deaths from 2008 - 2018, including selected opioids; (a) England and Wales [ONS, 2019] (b) Scotland [NRS, 2019] and (c) Northern Ireland [NISRA, 2019]

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
(a) England and Wales											
Total drug-misuse related deaths	2004	1976	1903	1737	1636	1957	2248	2479	2596	2503	2917
Heroin and morphine	897	880	791	596	579	765	952	1201	1209	1164	1336
Fentanyl	6	9	10	31	22	22	40	34	58	75	74
Fentanyl analogues	1	0	0	0	2	0	0	1	1	31	31
(b) Scotland											
Total drug-related deaths	574	545	485	584	581	527	614	706	868	934	1187
Heroin	261	270	193	147	135	143	219	238	326	314	375
Fentanyl	1	1	1	4	7	4	4	3	7	15	12
Acetylfentanyl	0	0	0	0	0	0	1	0	0	0	0
Alfentanil	0	0	0	0	0	0	0	0	0	1	0
(c) Northern Ireland											
Total drug-misuse related deaths	53	57	63	59	75	79	88	114	112	110	-
Heroin and morphine	6	9	16	17	24	25	11	27	25	24	-
Fentanyl	0	1	6	3	7	4	1	15	13	13	-
Fentanyl analogues	0	0	1	0	0	0	0	1	0	1	-

Notes:

Figures quoted for Northern Ireland, England and Wales are drug misuse-related deaths where the underlying cause is either drug abuse, drug dependence or drug poisoning and any of the substances controlled under the Misuse of Drugs Act 1971 are involved. Figures are for deaths registered, rather than deaths occurring in each calendar year.

For Scotland, numbers represent selected drugs or substances which were implicated in, or potentially contributed to, the cause of death [NRS 2019]

Data for 2018 is not available for Northern Ireland.

12.15. The National Programme on Substance Abuse Deaths (NPSAD) regularly receives information from coroners (on a voluntary basis) on deaths related to drugs in both addicts and non-addicts in England and Wales, Northern Ireland, the Channel Islands and the Isle of Man. Information was also received from the Scottish Crime and Drug Enforcement Agency between 2004 and 2011 and has been received from the General Register Office for Northern Ireland since 2004. To be recorded on the NPSAD

database there must be the presence of one or more psychoactive substance(s) directly implicated in the death, a history of dependence or abuse of drugs or the presence of controlled drugs at post-mortem.

- 12.16. NPSAD has provided data on deaths reported where a fentanyl was found at post-mortem and/or in the death for the period 1998 to 2018. There were 342 deaths reported involving a pharmaceutical fentanyl in 264 cases and a non-pharmaceutical fentanyl derivative (NPFd) in 78 cases. The first NPFd-related death was reported in 2015, with a steep increase in deaths in 2017 to outstrip those related to pharmaceutical fentanyls. Data for 2018 are incomplete but based on information received as of 7th May 2019, a substantial reduction in NPFd-related deaths is projected compared with 2017 (Table 4). NPSAD reports deaths according to the year when the death occurred. This contrasts with Office for National Statistics (ONS) data, which records deaths according to the year of registration (which may be later than the year the death occurred because of the time taken for coroners to investigate the death).
- 12.17. In the NPFd-fatalities reported between 2015 and 2017, carfentanil has been the most common (Table 5). In the NPFd cases, evidence of co-administration of multiple fentanyls (pharmaceutical or non-pharmaceutical) was common (43.5%), while other drugs of misuse (or their metabolites) were also frequently detected - especially cocaine (58%), heroin or morphine (56.5%) and benzodiazepines or Z-drugs (50.7%). Of the decedents where a non-pharmaceutical fentanyl had been found, 90% were males (mean age 37 years) and 10% females (mean age 45 years). Deaths involving pharmaceutical fentanyls were more equally distributed between males and females and affected older age groups. [Claridge *et al.*, 2019].

Table 4. Number of fentanyl-related fatalities in England reported to NPSAD for pharmaceutical and non-pharmaceutical fentanyls, 1998-2018

Year	Pharmaceutical fentanyl (which includes fentanyl, alfentanil, remifentanil and sufentanil)	Non-pharmaceutical fentanyl derivative (NPFDF) - All other fentanyl and fentanyl analogues (See list in table 5)
1998	1	
1999	1	
2000	0	
2001	1	
2002	2	
2003	4	
2004	0	
2005	1	
2006	3	
2007	3	
2008	5	
2009	14	
2010	6	
2011	15	
2012	15	
2013	25	
2014	21	
2015	30	2
2016	44	5
2017	42	62
2018	31	9
Total (1998-2018)	264	78
2018 (Projected full year)	40	10
Total (1998-2018, projected)	273	79

Note: For 2018 - figures relate only to fentanyl-related reports for concluded death inquests up until 7 May 2017. Due to the nature of the Coronial system, more deaths are expected to be reported for previous years, especially for 2018

Table 5. Cases reported to NPSAD for non-pharmaceutical fentanyl derivatives, 2015-2017

Non-pharmaceutical fentanyl derivative (NPFDF)	Number of cases where each NPFDF has been reported
Carfentanil	55
Para-Fluorobutyrfentanil	7
Butyrfentanil	6
Acetylfentanil	5
2-Fluorofentanil	2
Despropionylfentanil	2
Furanylfentanil	2
4-Fluorofentanil	1
Cyclopropylfentanil	1
Methoxyacetylfentanil	1
Ocfentanil	1
Unknown Fluorofentanil	1

Note: Note as more than one NPDF may be found in a single case, the sum of the NPDFs (84) is greater than the total number of NPDF cases (69).

- 12.18. In spite of the availability of these published and unpublished data, there remains uncertainty about precisely how many deaths are associated with fentanyl in the UK, because it is not always clear from the toxicology report whether fentanyl (or its analogues) were tested for. The apparent increases in the number of deaths involving fentanyl could be caused - or contributed to by - an increase in the number of cases where analytical testing for fentanyl analogues was conducted. Not all toxicology laboratories are equipped to test for fentanyl analogues; those that are, have become so on an *ad hoc* basis in response to localised outbreaks. As a result of the low concentrations involved and the range of possible variants, detection of fentanyl residues in post-mortem analysis is challenging and compounded by the expected low incidence. Consequently, fentanyl has not to date formed part of the traditional toxicology screen used in suspected overdose cases.
- 12.19. In heroin overdose cases, additional testing for fentanyl may not be deemed necessary. The decision will depend on funding, case circumstances and local working relationships between toxicologists, pathologists and coroners. Retrospective toxicological analysis of some cases previously categorised as 'heroin overdose deaths' has identified fentanyl. For example, over the first 6 months of 2017, the post mortem toxicology laboratory in Leicester analysed 97 samples from apparent heroin users where there was a convincing history of drug use close to the time of death but a low blood concentration of morphine, the major heroin metabolite. Of these, 25 were positive for synthetic fentanyl analogues; carfentanil was detected in all of these, as well as fentanyl in 20, butyrylfentanyl in 12, 4-flouro-butyrylfentanyl in 11 and furanylfentanyl in 2 [Hikin *et al.*, 2018]. This type of retrospective testing is not always possible, due to differences in storage and disposal of coronial toxicology samples between laboratories, and the stability of fentanyl in post-mortem samples [Concheiro *et al.*, 2018].
- 12.20. The United Nations Office on Drugs and Crime (UNODC) published recommended methods for the identification and analysis of fentanyl and its analogues in biological specimens in 2017 [UNODC, 2017].
- 12.21. Drug testing kits are commercially available and could be used by drug users to detect the presence of fentanyl in heroin. Some have demonstrated sensitivity and specificity in detecting fentanyl and may also detect some important fentanyl analogues such as carfentanil, acetylfentanyl, and butyrylfentanyl [McGowan *et al.*, 2018]. Use of these products can alter drug-use behaviour [Peiper *et al.*, 2019] but further evidence is needed of the sensitivity and specificity of available products and the impact of their use on risk of overdose.

12.22. PHE have recognised the threat from potent opioids and issued guidance to local commissioners and service providers on appropriate responses. These include appropriate THN provision, enhancing access to drug treatment services, effective local drug information systems and drug death reviews. Advice to users has also been made available [PHE, 2018].

12.23. In December 2016, the ACMD published an independent report on reducing opioid-related deaths in the UK [ACMD 2016a]. Recommendations from this report, reproduced in Annex 4, are also pertinent to preventing drug deaths caused by fentanyl and fentanyl analogues.

[paragraph 12.24 has been redacted from the published version of this report]

13. UK Law Enforcement

13.1. In early 2017, UK law enforcement became aware of a substantial increase in opioid-related deaths in the North of England where fentanyl or its analogues were found by toxicology testing. In April 2017, the NCA initiated high-priority Project RANSEL to investigate and coordinate the UK law enforcement response. The project team work closely with law enforcement partners from the US, Canada and across Europe to identify those responsible for the importation and supply of fentanyl and its analogues.

13.2. Almost 100% of fentanyl arrives in the UK via postal services in small amounts from China, either directly or via EU countries. It has been identified that there are largely two distinct lines of supply by which fentanyl analogues are reaching illicit drug users in the UK:

- online supply - principally via darknet vendors, but also in some cases direct from Chinese manufacturers (although the latter source tends to be mainly used by suppliers seeking supply quantities)
- traditional drug supply chains e.g. for heroin, where fentanyl or an analogue has been added to fortify the dose supplied by enhancing its

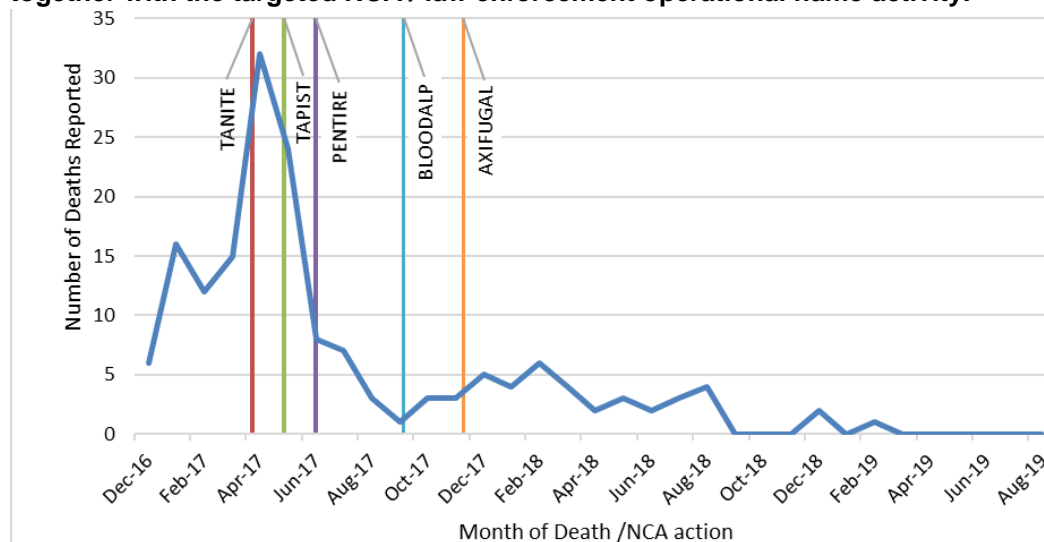
opioid potency. The potential risk that this could include County Lines heroin supplies is currently being monitored by the NCA.

13.3. Fentanyl analogues can be readily obtained from online suppliers - many of whom are darknet vendors - on encrypted market places based in The Onion Router (Tor, open source software for enabling anonymous communication and cryptocurrency transactions). This mode of supply presents a considerable risk as it is not constrained by geographical boundaries and deliveries to customers are concealed among the sheer volume of domestic and international fast parcel traffic. To combat this threat, intelligence is being developed into the active darknet markets. Several significant darknet UK fentanyl suppliers have been prosecuted in the last year.

13.4. In criminal prosecutions, the additional harms associated with fentanyls have been recognised and Crown Prosecution Service (CPS) guidance for cases involving fentanyls requires prosecutors to alert courts to their potential impact and to provide expert witness testimony to explain the relative harm of the materials as compared to heroin [CPS, 2019]. The Sentencing Council has provided guidance on the appropriate sentences in cases involving newer drugs such as synthetic opioids [Sentencing Council, 2019].

13.5. As of August 2019, Project RANSEL had identified 166 fentanyl-related mortalities since December 2016, reaching across 33 UK police force areas. This combined law enforcement action to identify those dealing on the darknet, international importations of fentanyl, the prosecution of suppliers together with the take down of darknet sites, has resulted in the significant reduction of fentanyl related deaths (Figure 2). However, the NCA continues to monitor the situation and prosecute importers and suppliers where possible.

Figure 2: Timeline of Project RANSEL reported fentanyl and fentanyl analogue-related deaths, together with the targeted NCA / law enforcement operational name activity.



14. Legal status of fentanyls - UK

14.1. All the International Narcotics Control Board (INCB) listed materials are controlled within the United Kingdom as Class A drugs, in accordance with the UK's status as a signatory of the relevant UN Convention. Control is either by name or by virtue of a generic control, which was added to the UK's Misuse of Drugs Act in 1986 (SI 1986/2230). This amendment added carfentanil and lofentanil by name to the list of Class A drugs (carfentanil was included on INCB list in 2018 [INCB, 2019] and lofentanil remains unlisted). The generic control included within the amendment addresses a very wide range of modifications to the various parts of the fentanyl structure, as follows:

“Any compound.....structurally derived from fentanyl by modification in any of the following ways, that is to say,

- (i) By replacement of the phenyl portion of the phenethyl group by any heterocycle whether or not further substituted in the heterocycle;*
- (ii) By substitution in the phenethyl group with alkyl, alkenyl, alkoxy, hydroxy, halogeno, haloalkyl, amino or nitro groups;*
- (iii) By substitution in the piperidine ring with alkyl or alkenyl groups;*
- (iv) By substitution in the aniline ring with alkyl, alkoxy, alkylendioxy, halogeno or haloalkyl groups;*
- (v) By substitution at the 4- position of the piperidine ring with any alkoxy carbonyl or alkoxyalkyl or acyloxy group;*
- (vi) By replacement of the N-propionyl group by another acyl group”*

14.2. This generic control has proved to be extremely effective in ensuring that the new 'designer' versions of fentanyl being encountered are already controlled as Class A drugs. Of the 34 fentanyl-related materials which had been reported to the EMCDDA up to the end of August 2019, all but eight are covered by the UK's generic control. Of these eight, two are a precursor (2F-ANPP) and a pre-precursor (1-phenethyl-4-hydroxypiperidine), while five are benzyl fentanyls (see below) which have significantly lower potencies than their phenethyl fentanyl equivalents. Further information about fentanyl precursors controls is provided in Annex 6.

14.3. The remaining material is para-hydroxybutyrylfentanil, reported in 2018. This is outside the scope of the UK generic as the addition of a hydroxyl group to the aniline ring is not covered by para (iv). The potency of this material is not yet known, but it can be expected to be active to some degree at the μ -opioid receptor.

15. Conclusions

Conclusion 1: Fentanyl and its analogues are potent compounds that carry a high risk of accidental overdose that may be fatal. Infiltration of fentanyls into the heroin supply chain in the United States and Canada has been responsible for substantial increases in drug-related deaths.

Conclusion 2: The risk to public health from fentanyls may be lower in the UK than in North America because there is a smaller population of people who have become habituated to strong opioids. There is, however, limited information available about diversion rates and misuse of pharmaceutical fentanyls in the UK.

Conclusion 3: Episodes of fentanyl toxicity and deaths in the UK have been sporadic and have not approached the very high numbers seen in North America. However, rates of registered deaths involving fentanyls have recently increased and may be under-estimated because sufficiently detailed forensic analysis of drug causes is sometimes not carried out. Consequently, the role of a fentanyl in the death may not be recognised.

Conclusion 4: There remains an ongoing risk of fentanyls and other new synthetic opioids increasingly infiltrating the UK heroin market and increasing rates of drug-related deaths. The long-standing UK generic control on fentanyls has proved to be robust and almost all 'designer' fentanyl variants being encountered are automatically controlled in the UK as Class A drugs. There are a small number that are not controlled, although these are largely of lower potency and carry a lower risk of overdose. Most fentanyl precursors are also controlled, with some exceptions.

16. Recommendations

Recommendation 1: Research should be commissioned to study diversion and non-medical use of strong opioids to identify trends, drug products involved and populations at risk.

Leads: National Institute for Health Research (NIHR), PHE

Measure of outcome: A themed topic to be developed by NIHR and any other relevant bodies in the next 12 months to make information available on diversion of prescribed opioids, especially products most affected.

Recommendation 2: Government departments should conduct a full review of international drug strategy approaches to fentanyl markets, in particular, the North American experience, and consider interdiction controls that can be applied to the UK situation.

Leads: Border Force, Home Office, Department of Health and Social Care (DHSC)

Measure of outcome: A written report from each of the leads with a UK specific plan committing to fund recommended initiatives, technologies or investments in staffing capabilities.

Recommendation 3: Ensure that health professionals are trained in the appropriate therapeutic use of strong opioids, as described in the ‘Opioids Aware’ resource and the forthcoming NICE guidance on management of chronic pain.

Leads: DHSC in England and Departments of Health in devolved administrations, General Medical Council and equivalents for non-medical prescribers, Medical Royal Colleges, Health Education England, Clinical Commissioning Groups (and equivalents for devolved administrations).

Measure of outcome: Number of health professionals who have completed relevant training. Reduced inappropriate (e.g. long-term) prescribing of strong opioids, reducing risk of dependency and diversion.

Recommendation 4:

- a) Toxicology analysis of samples of all deaths related to drug poisoning should include analysis for fentanyl and fentanyl analogues as non-systematic screening hinders our capacity to understand trends in drug deaths.
- b) Toxicology reports from all deaths related to drug poisoning should include a clear statement as to whether fentanyl and/or its analogues were included in the testing. Importantly it should be made explicit if fentanyl and/or its analogues have not been tested for. This would enable meaningful monitoring of trends in fentanyl-associated deaths.

Leads: Coroners in England, Wales and Northern Ireland and procurators fiscal in Scotland.

Measure of outcome: All post-mortem drug testing to include testing of fentanyl and fentanyl analogues on the testing panel or a statement that testing has not been done. If these recommendations are implemented, agencies monitoring drug-related deaths will be able to report fentanyl-associated deaths as ‘a percentage of those tested for fentanyls’.

Recommendation 5:

- a) Research should be commissioned to monitor the local and national prevalence of fentanyl and fentanyl analogues in:

- i) drug seizures, including heroin preparations and counterfeit medicines;
 - ii) non-fatal episodes of heroin toxicity requiring hospital treatment.
- b)** Increased funding should be made available to the Defence, Science and Technology Laboratory Forensic Early Warning System (DSTL FEWS) programme to increase capacity to analyse un-adopted police and border force seizures.

Leads: NIHR, PHE, Home Office

Measure of outcome: Regularly published reports available containing information about fentanyl contamination of drug products in the UK (including in different geographic areas) and on involvement in non-fatal episodes of toxicity.

Recommendation 6: Agencies with responsibilities relating to drugs of misuse should monitor the international situation and share available UK data. There should also be a comprehensive early warning system which has access to up to date consolidated UK-wide drug misuse data sets.

Leads: PHE, DHSC (and equivalents in devolved administrations), Home Office

Measure of outcome: Better surveillance information available and earlier detection of drug misuse issues with public health consequences.

Recommendation 7: If materials are encountered in the UK or Europe that retain potency but fall outside the UK generic control on fentanyls, a small amendment to that generic control should be applied to address these.

Leads: Home Office

Measure of outcome: Legal control using the Misuse of Drugs Act in place in the UK for all fentanyl analogues encountered in Europe.

Recommendation 8: Following a consultation with the research community, the Home Office should expand the precursor controls to cover simple variants of ANPP (see Annex 6), the immediate precursor to fentanyl. It is recommended that paragraphs (i) to (v) of the text of the existing generic control on fentanyls be also applied in the precursor legislation, that is that the entry for ANPP be amended to cover:

“Any compound.....structurally derived from ANPP by modification in any of the following ways, that is to say:

- (i) By replacement of the phenyl portion of the phenethyl group by any heterocycle whether or not further substituted in the heterocycle;

- (ii) By substitution in the phenethyl group with alkyl, alkenyl, alkoxy, hydroxy, halogeno, haloalkyl, amino or nitro groups;
- (iii) By substitution in the piperidine ring with alkyl or alkenyl groups;
- (iv) By substitution in the aniline ring with alkyl, alkoxy, alkylendioxy, halogeno or haloalkyl groups;
- (v) By substitution at the 4- position of the piperidine ring with any alkoxy carbonyl or alkoxyalkyl or acyloxy group”

[Note: para (vi) of the fentanyl generic refers to the propionyl group being replaced by another acyl group, but this feature is absent in ANPP and so is not required here]

In order also to control the benzyl analogues of fentanyl as precursors (see Annex 7), the new control described above should be further expanded by adding a paragraph:

(i)(a) “By replacement of the phenethyl group by a benzyl group;”

And by expansion of para (ii) to:

(ii) By substitution in the phenethyl or benzyl group with alkyl, alkenyl, alkoxy, hydroxy, halogeno, haloalkyl, amino or nitro groups”

Lead: Home Office

Measure of outcome: Prevention of illicit fentanyl manufacture in the UK and overseas without impacting on legitimate uses

Annex 1: Primary care prescribing (prescription numbers) of fentanyl products in England, 2014-2018 (NHS Digital, 2019)

Chemical Substance	Product type	2014	2015	2016	2017	2018	Grand Total
Alfentanil Hydrochloride	Parenteral	3,634	3,793	4,292	4,387	4,569	20,675
	Nasal Spray	219	200	222	317	609	1,567
Fentanyl	Patch	1,169,590	1,193,057	1,210,571	1,163,164	1,085,853	5,822,235
	Lozenge	17,595	16,790	16,101	15,219	13,886	79,591
	Sublingual Tablet	10,336	10,365	9,834	9,130	9,312	48,977
	Buccal Tablet	6,769	6,918	8,168	8,739	7,359	37,953
	Nasal Spray	1,720	1,969	1,523	1,594	1,175	7,981
	I/V	286	421	407	508	598	2,220
	Buccal Film	77	58	-	-	-	135
Remifentanil Hydrochloride	Parenteral	-	1	-	-	-	1
Grand Total		1,209,940	1,233,151	1,250,711	1,202,550	1,122,763	6,019,115

Annex 2: NPIS data on fentanyls, fentanyl analogues and other new synthetic opioids

(1) TOXBASE accesses for heroin, fentanyl, fentanyl analogues and other new synthetic opioids, 2014-2018

Ingredient	TOTAL	2014	2015	2016	2017	2018
Heroin (and synonyms)	26,729	5,182	5,764	5,244	5,173	5,366
Fentanyl	2,683	405	375	508	703	692
Carfentanil	461	6	8	34	337	76
Alfentanil	79	9	7	17	28	18
Remifentanil	55	6	6	16	19	8
Acetyl fentanyl	47	0	3	11	11	22
Furanyl fentanyl	31	0	0	9	16	6
3-methylfentanyl	21	8	5	2	5	1
Ocfentanil	20	4	4	5	4	3
Acryloylfentanyl	18	0	0	3	7	8
U-47,700	18	0	0	6	7	5
Valerylfentanyl	17	0	0	7	5	5
Methoxyacetylfentanyl	15	0	0	0	8	7
MT-45	14	3	0	1	6	4
2-fluorofentanyl	13	0	0	1	7	5
Benzoylfentanyl	9	0	0	0	2	7
Sufentanil	9	0	0	0	7	2
Benzodioxolefentanyl	8	0	0	0	2	6
Tetrahydrofuranfentanyl	8	0	0	0	3	5
4-chloro-isobutyrfentanyl	4	0	0	0	3	1
3-Phenylpropanoylfentanyl	2	0	0	0	1	1
4-fluoro-butyrfentanyl	2	0	0	0	2	0
Cyclopentylfentanyl	2	0	0	0	0	2
Cyclopropylfentanyl	1	0	0	0	0	1

(2) NPIS telephone enquiries involving heroin, fentanyl and fentanyl analogues, 2014-2018

(a) All enquiries

Ingredient	TOTAL	2014	2015	2016	2017	2018
Heroin	544	107	131	109	89	108
Fentanyl patch	163	25	38	24	26	29
Fentanyl (other)	31	4	1	5	12	6
Fentanyl lozenge	4	0	1	1	1	1
Other fentanyl analogues	3	0	0	2	1	0
Carfentanil	4	0	0	1	3	0

(b) Enquiries logged as 'recreational misuse'

Ingredient	TOTAL	2014	2015	2016	2017	2018
Heroin	228	38	54	45	37	54
Fentanyl patch	5	0	1	1	1	0
Fentanyl (other)	9	2	0	1	5	0
Fentanyl lozenge	0	0	0	0	0	0
Other fentanyl analogues	3	0	0	2	1	0
Carfentanil	1	0	0	0	1	0

Annex 3: Fentanyl analogues notified in the EMCDDA EU Early Warning System on new psychoactive substances, 2013-2019

2013	Carfentanil, ocfentanyl
2014	4-Fluorobutyrylfentanyl, butyrylfentanyl, acetylfentanyl
2015	4-methoxybutyrylfentanyl, furanylfentanyl
2016	Valerylfentanyl, acryloylfentanyl, 2-fluorofentanyl, 4-chloroisobutyrylfentanyl, 4-fluoroisobutyrylfentanyl, 3-fluorofentanyl, 2-methoxyacetylfentanyl, tetrahydrofuranylfentanyl
2017	Cyclopentylfentanyl, benzodioxolefentanyl, benzoylfentanyl, 3-phenylpropanoylfentanyl, tetramethylcyclopropylfentanyl, cyclopropylfentanyl, acetylbenzylfentanyl, benzoyloxybenzylfentanyl, benzylfentanyl, thiophenefentanyl
2018	3-Fluoromethoxyacetylfentanyl, furanylbenzylfentanyl, 4-fluorocyclopropylbenzylfentanyl, 4-hydroxybutyrylfentanyl, 3-methylcrotonylfentanyl, 2-methylfentanyl
2019 (up to August 2019)	4F-furanylfentanyl

Annex 4: ACMD recommendations for reducing opioid-related deaths in the UK (December 2016)

1. Improving the current processes by creating data standards for local reporting that feed into national systems. This may include: coroners reporting; toxicological assessments to understand poly-substance use; local partnership investigations and information sharing on drug-related deaths (DRDs) and non-fatal overdoses; and strengthening links between national datasets including death registrations and national treatment monitoring systems
2. Central and local governments implement strategies to protect the current levels of investment in evidence-based drug treatment which can enable people to achieve a range of recovery outcomes, including sustained abstinence from opioids
3. Central and local governments continue to invest in high-quality Opioid Substitution Therapy (OST) of optimal dosage and duration, delivered together with interventions to help people achieve wider recovery outcomes including health and well-being, in order to continue to reduce rates of Drug Related Deaths.
4. Drug treatment services should follow national clinical guidelines on OST and provide tailored treatment for individuals for as long as required
5. Central government funding should be provided to support heroin-assisted treatment for patients for whom other forms of OST have not been effective
6. That naloxone is made available routinely, cheaply and easily to people who use opioids, and to their families and friends
7. Consideration is given – by the governments of each UK country and by local commissioners of drug treatment services – to the potential to reduce Drug Related Deaths and other harms through the provision of medically-supervised drug consumption clinics in localities with a high concentration of injecting drug use
8. Central and local governments provide an integrated approach for drug users at risk of Drug Related Death, and prioritise funding and access to physical and mental health and social care services
9. Governments fund research to fill important gaps in the literature on the causes and prevention of opioid-related deaths

Annex 5: International legal status of fentanyl

International Narcotics Control Board (INCB)

A number of fentanyl, both licensed pharmaceuticals and non-pharmaceutical 'designer' variants, are named in the INCB's 'Yellow list' of narcotics under international control (http://www.incb.org/documents/Narcotic-Drugs/Yellow_List/57th_edition/57th_edition_YL_ENG.pdf). As at July 2017, the internationally-controlled fentanyl variants listed in Schedule I of the 1961 Convention were the pharmaceuticals:

- Alfentanil
- Fentanyl
- Remifentanil
- Sufentanil

And the non-pharmaceutical variants:

- Acetyl α -methylfentanyl*
- Acetyl fentanyl* (added in March 2016)
- Thiofentanyl*
- β -Hydroxythiofentanyl
- β -Hydroxy-3-methylthiofentanyl
- Butyryl fentanyl (added in March 2017)
- 3-Methylfentanyl*
- 3-Methylthiofentanyl*
- para-Fluorofentanyl*

Note: The asterisked materials are also listed in Schedule IV of the Convention as being of particular concern, as are:

- α -Methyl fentanyl
- α -Methyl thiofentanyl
- β -Hydroxyfentanyl
- β -Hydroxy-3-methyl fentanyl ('Ohmefentanyl')

In March 2018, the INCB added 6 more fentanyl to Schedule I of the 1961 Convention:

- Acryl fentanyl
- Carfentanil (also included in Schedule IV)
- Para-Fluoroisobutyrylfentanyl
- Furanyl fentanyl
- Ocfentanil
- Tetrahydrofuranylfentanyl

In March 2019, a further 4 fentanyl were added:

- Cyclopropyl fentanyl
- Methoxyacetyl fentanyl
- ortho-Fluoro fentanyl
- para-Fluoro butyrylfentanyl

This means that 25 fentanyl variants are under international control, with 11 of these also listed in Schedule IV as being of particular concern. However, many other variants have already been reported by the EMCDDA as having been encountered within Europe. Two further fentanyl variants - crotonyl fentanyl and valeryl fentanyl - are currently listed for consideration for international control.

United States

The United States drug control system is founded on the Controlled Substances Act (CSA), which lists individual substances, and the Federal Analogue Act, which enables control of materials which can be shown to be “substantially similar” (in chemistry and effect) to a material already listed in Schedule I or II of the CSA. As the hazard presented by fentanyls has been appreciated and a series of new variants have appeared on the US market, the US has responded by the rapid enactment of a series of orders to place materials into Schedule I of the CSA. These have included: -

- 2015: Acetyl fentanyl
- 2016: Furanyl fentanyl, Butyryl fentanyl, β-Hydroxy thiofentanyl
- 2017: Acryl fentanyl, ortho-Fluorofentanyl, Methoxyacetyl fentanyl, Tetrahydrofuranylfentanyl, 4-Fluoroisobutyryl fentanyl
- 2018: Cyclopentyl fentanyl, Valeryl fentanyl, para-Fluorobutyryl, para-Methoxybutyryl fentanyl, para-Chloroisobutyryl fentanyl, Isobutyryl fentanyl, Cyclopropyl fentanyl, Ocfentanil

As the broad range of potential variants of fentanyl has become apparent, the US changed its approach to control, moving away from attempts to control individual compounds. In February 2018, they adopted a temporary (2-year duration) generic control based on the UK’s generic control, as follows:

Any substance.....that is structurally related to fentanyl by one or more of the following modifications:

- (A) Replacement of the phenyl portion of the phenethyl group by any monocycle, whether or not further substituted in or on the monocycle;*
- (B) Substitution in or on the phenethyl group with alkyl, alkenyl, alkoxy, hydroxyl, halo, haloalkyl, amino or nitro groups;*
- (C) Substitution in or on the piperidine ring with alkyl, alkenyl, alkoxy, ester, ether, hydroxyl, halo, haloalkyl, amino or nitro groups;*
- (D) Replacement of the aniline ring with any aromatic monocycle, whether or not further substituted in or on the aromatic monocycle; and/or*
- (E) Replacement of the N-propionyl group by another acyl group.*

Clauses (A), (B) and (E) closely mirror the wording of clauses (i), (ii) and (vi) of the UK’s generic control. However, US clause (C) places a broader control on

substitution on the piperidine ring than those specified by the UK's clauses (iii) and (v). In addition, US clause (D) covers replacement of the aniline ring which is not addressed by the UK's control.

China

China is widely reported to be the major source of the fentanyls entering North American and European markets, so the legal status of fentanyl variants within China has a significant bearing on the materials being encountered overseas. China has acceded to the UN's drug Conventions and has aligned its controls of fentanyls with those listed in the international system. China has also included a number of other fentanyl variants to its list of controlled materials, in advance of the requirement to do so resulting from the UN Narcotics Convention.

Recent additions to the list of fentanyl variants controlled in China include:

October 2015: Acetyl, Butyryl, β -Hydroxythio, para-Fluorobutyryl, isoButyryl and Ocfentanil

February 2017: Carfentanil, Furanylfentanyl, Acrylfentanyl and Valerylfentanyl

The effect of these controls has been apparent in the range of substances being advertised for sale on Chinese websites and on the evolution of fentanyl variants being seen in Western countries.

On 1 April 2019, China announced that it would, with effect from 1 May 2019, control all fentanyl-related variants which do not have established medical, industrial or scientific uses. The scope of this control is based on a generic, closely based on the American generic, covering:

1. Use of acyl groups instead of propionyl
2. Replacing the phenyl group attached to the nitrogen atom by any substituted or unsubstituted monocyclic aromatic group
3. Substitution by an alkyl, alkenyl, alkoxy, ester, ether, hydroxyl, halogen, halogenated alkyl, amino or nitro
4. Replacement of phenethyl by any other group (except hydrogen)"

European Union (EU)

Under Council Decision 2005/387/JHA addressing NPS, the EU operates its own system to assess psychoactive materials being encountered within Europe that are not already under international control. Where considered appropriate, an Implementing Decision can be issued, requiring all member states to bring materials under control. As is the case with the UN's system, this process reviews individual substances, rather than groups of materials.

Fentanyl variants which have recently been assessed by the EU system include:

2017: Acrylfentanyl, Furanylfentanyl, Tetrahydrofuranylfentanyl, para-Fluoro isobutyrylfentanyl and Carfentanil

2018: Methoxyacetylfentanyl and Cyclopropylfentanyl

All of these are already controlled within the UK and have now become controlled under the United Nations system (see above).

Annex 6. Fentanyl precursor controls

The 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropics includes controls on trade in certain chemicals which are precursors for controlled drugs. In October 2017 the United Nations' Commission on Narcotic Drugs, in response to a joint approach by the United States and China, added two substances which are precursors for fentanyl and many of its variants when using the 'Siegfried process' to the Schedule 1 list of the most stringently controlled precursor materials (https://www.incb.org/incb/en/news/press-releases/2017/press_release_20171018.html). These were the immediate precursor to fentanyl ANPP, and ANPP's own precursor NPP. The EU - and therefore the United Kingdom - have enacted the controls necessary to comply with the UN's requirements through the relevant legislation (The Controlled Drugs (Drug Precursors) (Intra-Community Trade) Regulations 2008 and The Controlled Drugs (Drug Precursors) (Community External Trade) Regulations 2008).

ANPP, the immediate precursor to fentanyl, can be converted into a wide variety of fentanyl derivatives by substituting other acyl chlorides in place of the propionyl chloride which is used to produce fentanyl in the final stage of the Siegfried method. For example, at its simplest, the three carbon propionyl chain can be shortened to a two-carbon chain to produce acetyl fentanyl, or lengthened to a four carbon chain to produce butyryl fentanyl. Production of this type of fentanyl variant will be impacted by the new precursor controls.

However, there are potential limitations to the effectiveness of these controls:

- As with all precursor controls, there is a risk that the controlled precursors can in turn be synthesised from uncontrolled 'pre-precursors', or that alternative synthetic routes such as the Janssen method using other precursors can be adopted.
- More significantly, a number of fentanyl derivatives are prepared using variants of ANPP and several of the fentanyl variants which have been identified by the EMCDDA have structural modifications derived from modified versions of the ANPP precursor. Most commonly, these substances have been derived from versions of ANPP halogenated on the aniline ring, and have to date included o-fluoro and m-fluoro fentanyl, p-fluorobutyryl fentanyl, p-chloroisobutyryl fentanyl and p-fluoroisobutyryl fentanyl. The o-fluorinated form of the ANPP precursor, used to produce the potent o-fluorinated form of 'Siegfried process' variants, was reported as having been seized entering France and Germany in 2015. Similarly, it is known that modification of the piperidine ring by adding a methyl group in the 3- position can significantly enhance the potency of fentanyls. For example, *cis*-3-methyl fentanyl is several times more potent than fentanyl and was one of the first illicitly-produced fentanyls to appear as a drug of abuse in the United States in the 1970s. It would therefore be logical to expand the precursor control to include such variants of ANPP.
- In addition, given the potency of the fentanyls and the relatively small quantities required to support illicit activities, the controls available under

precursor legislation, which were primarily designed to control and manage legitimate trade by placing licensing and reporting responsibilities on those involved in supply of the listed substances, may be insufficient to prevent illegal trafficking. For example, possession of precursors is not an offence. There is precedent for precursors to be controlled directly via the Misuse of Drugs Act as, prior to the introduction of the precursor Regulations, some direct precursors of controlled drugs were listed within the Act. For example, several precursors to methadone and pethidine are listed within the UN Convention on Narcotic Drugs and are named within the UK Misuse of Drugs Act as Class A drugs.

Annex 7. Comparative potencies of fentanyl variants

The relative potencies and operational characteristics of those fentanyls approved for pharmaceutical use are well documented. The many illicit variants have been much less well-studied; however, some information sources are available:

- Some pharmacological test data on ‘designer’ forms do exist (see for example in Annex 2), but this is primarily from *in-vitro* or animal studies, which may not be fully predictive of their effect on humans. See also Higashikawa & Suzuki, 2008
- Emerging findings from anti- and post-mortem toxicology are providing data on the relative levels of different fentanyl variants found in human users, but these are hard to interpret as the findings from fatal and ‘driving under the influence’ cases overlap and are thought to be confounded by the tolerance to fentanyls known to develop rapidly amongst regular users.
- There are also informal comparative evaluation reports on drug discussion websites where users report (very subjectively) their experiences.

However, from published pharmaceutical studies of structure-activity relationships, a number of modifications to the fentanyl structure can be expected to increase potency by enhancing interaction with the μ opioid receptor or increasing duration by inhibiting metabolic breakdown. Known potency-enhancing modifications include the addition of a methyl group at the 3- position of the piperidine ring (particularly when in the *cis*- arrangement relative to the anilido group), an hydroxyl group at the β - position of the phenethyl chain, a halogen atom on the aniline or phenethyl rings, especially a fluorine atom at the o-position of the aniline ring, and, particularly, a carbomethoxy or methoxymethyl group at the 4-position of the piperidine ring. An alpha-methyl group on the phenethyl chain inhibits enzymatic degradation and so increases duration of effect.

Combinations of these modifications can produce extremely potent materials. Carfentanil, for example, is carbomethoxy fentanyl, and the even more potent lofentanil is 3-methyl carfentanil, while ohmefentanyl combines both the 3-methyl and β -hydroxy modifications of fentanyl.

Based on the known information and extrapolating from other sources, fentanyl analogues can be grouped into five types:

i) ‘Super potent’ materials

A small group of fentanyl analogues such as carfentanil, lofentanil (3-methyl carfentanil) and some stereoisomers of 3-methyl fentanyl and ohmefentanyl (β -hydroxy-3-methylfentanyl) are very significantly more potent than fentanyl and therefore present a very severe risk of accidental overdose. For context, at post-mortem, typical levels of morphine in blood associated with fatalities are in excess of 50 ng/ml, for fentanyl greater than 3 ng/ml and for carfentanil greater than 0.1 ng/ml. Additional modifications of these structures have been reported to be able to produce even more potent materials.

Although 3-methylfentanyl appeared in the US as one of the original ‘designer’ variants in the late 1970s/1980s, and has until recently been circulating in Estonia,

carfentanil is the only example of such materials currently being encountered in the illicit drug field, including in the UK.

All 'super potent' variants are within the scope of the UK's generic control and are therefore Class A drugs.

ii) Halogenated materials

Some variants reported by the EMCDDA are simple halogenated forms of fentanyl, with the halogen atom added to the aniline or phenethyl ring, intended either to provide some additional potency (fluorination at the ortho-position of the aniline ring can produce significant increases) or to avoid substance-specific legislation.

EMCDDA notifications of this type include:

- o-Fluorofentanyl
- m-Fluorofentanyl

Note: p-Fluorofentanyl is named in the UN Convention and is therefore already controlled internationally.

Halogenated variants of fentanyl, synthesised from halogenated forms of the ANPP precursor, are covered by sub-paras (ii) and (iv) of the UK's generic control as Class A drugs.

iii) 'Siegfried process' derived materials

By far, the majority of the variants of fentanyl being reported in recent years simply have the propionyl group of fentanyl replaced by other small acyl groups. These variants can be produced by the 'Siegfried' synthetic route by using a different acyl chloride in the final, room-temperature, conversion of the immediate precursor (ANPP) to the new variant.

Pharmaceutical structure-activity studies had identified the propionyl group present in fentanyl as being optimal in terms of potency and duration of effect and, from available data and user reports, most variants of this type are less potent than fentanyl itself. The main rationale to produce a continuing stream of such 'designer' versions is therefore presumably to avoid legal controls which name specific compounds. However, most 'Siegfried' variants are still significantly more potent than morphine and retain the increased risk of overdose associated with fentanyl.

EMCDDA notifications of these types of materials to date have included fentanyls with the following groups replacing propionyl (where described, potencies are primarily based on subjective user reports; for more recently reported materials, such feedback is sparse):

- Butyryl- (reported to be shorter acting and one quarter the potency of fentanyl)
- Acetyl- (reported to be one fifth the potency of fentanyl)
- para-Methoxybutyryl-
- Furanyl- (reported to be one fifth the potency of fentanyl)
- Valeryl- (reported to be less potent than butyryl)
- Acryl- (potency similar to or slightly greater than fentanyl)

- 2-Methoxyacetyl- (similar to or slightly more potent than fentanyl)
- Tetrahydrofuranyl-
- Cyclopentyl-
- Benzodioxazole-
- 3-Phenylpropionyl-
- Tetramethylcyclopropyl-
- Cyclopropyl-
- Thiopheneyl-
- 3-Methylcrotonyl-

In the UK, all are covered by clause (vi) of the generic control and are therefore Class A drugs.

iv) Halogenated ‘Siegfried process’ materials

Some EMCDDA-reported variants combine replacement of the propionyl group with additional halogenation of the phenyl ring, which can be expected to enhance potency:

- o-Fluoromethoxyacetyl- (‘Ocfentanil’ – reportedly 1.5 to 2.5 times more potent than fentanyl)
- p-Fluorobutyryl-
- p-Chloroisobutyryl-
- p-Fluoroisobutyryl-
- 3-Fluoromethoxyacetylfentanyl (the 3-fluoro positional isomer of Ocfentanil)
- 4-Fluorofuranyl fentanyl

These too are all covered by the UK’s generic control as Class A drugs.

v) Less potent variants outside the UK generic control

Recent EMCDDA notifications have included a number of benzyl fentanyl. These variants have the two-carbon chain of the phenethyl group shortened to a single carbon (as also seen in thienyl fentanyl). The variants reported were:

- Benzyl-
- Benzyloyl benzyl-
- Acetyl benzyl-
- 4-Fluorocyclopropyl benzyl-
- Furanyl benzyl-

This modification of the fentanyl structure is not covered by the UK generic control. However, the modification appears to result in a very significant reduction in potency. In 1985, the United States used temporary scheduling to place benzyl and thienyl fentanyl, along with a number of other fentanyl, into Schedule I of their Controlled Substances Act, but subsequently allowed the control on these two materials to lapse as testing had indicate that they were “essentially inactive” (https://www.deadiversion.usdoj.gov/fed_regs/rules/2010/fr06292.htm). Although not presenting the same degree of risk as other fentanyl variants, there may be sufficient

activity for these substances to merit control under the Psychoactive Substances Act 2016 - testing to assess this is being commissioned.

Note: *Benzyl fentanyl is an intermediate in the original Janssen synthetic route, the final stages of which involve removal of the benzyl group to produce norfentanyl, followed by replacement by the phenethyl group. These materials can therefore be regarded as precursors in the Janssen method.*

Annex 8 – List of Abbreviations used in this report

ACMD	Advisory Council on the Misuse of Drugs
ANPP	4-anilo-N-phenethylpiperidine
CDC	Centers for Disease Control and Prevention
CFR	Council on Foreign Relations
CPS	Crown Prosecution Service
CSA	Controlled Substances Act
DEA	Drug Enforcement Administration
DHSC	Department of Health and Social Care
DSTL	Defence, Science and Technology Laboratory
FEWS	Forensic Early Warning System
EMC	Electronic Medicines Compendium
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU	European Union
FBI	Federal Bureau of Investigation
FIRMR	Fentanyl-Induced Respiratory Muscle Rigidity
HCEC	House Committee on Energy and Commerce
IMFs	International Mail Facilities
INCB	International Narcotics Control Board
INN	International Non-proprietary Names
IONA	Identification Of Novel psychoactive substances
NCA	National Crime Agency
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIDA	National Institute on Drug Abuse
NIHR	National Institute for Health Research
NISRA	Northern Ireland Statistics and Research Agency
NPFD	non-pharmaceutical fentanyl derivative
NPIS	National Poisons Information Service
NPP	N-phenethylpiperidone
NPS	Novel Psychoactive Substances
NPSAD	The National Programme on Substance Abuse Deaths
NRS	National Records of Scotland
NSC	National Safety Council
NSOs	New Synthetic Opioids
ONS	Office for National Statistics
ONDCP	Office of National Drug Control Policy
OST	Opioid Substitution Therapy
PHE	Public Health England
PIL	Prescription Interdiction and Litigation
RCAFPM	Royal College of Anaesthetists, Faculty of Pain Medicine
THN	Take Home Naloxone
UK	United Kingdom
UNODC	The United Nations Office on Drugs and Crime

US	United States
USCC	United States – China Economic and Security Review Commission
USD	US Dollars
VMD	Veterinary Medicines Directorate
WEDINOS	Welsh Emerging Drugs and Identification of Novel Substances Project
WHO	World Health Organisation

Annex 9 – ACMD membership, at time of publication

Dr Kostas Agath	Consultant Psychiatrist (addictions), CGL Southwark
Dr Owen Bowden-Jones	Chair of ACMD, Consultant psychiatrist, Central North West London NHS Foundation Trust
Dr Anne Campbell	Senior lecturer in social work and Co-Director of the drug and alcohol research network at Queens University Belfast
Mr Mohammed Fessal	Chief Pharmacist, CGL
Dr Emily Finch	Clinical Director of the Addictions Clinical Academic Group and a consultant psychiatrist for South London and Maudsley NHS Trust
Mr Lawrence Gibbons	Head of Drug Threat – NCA Intelligence Directorate – Commodities
Dr Hillary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Professor Graeme Henderson	Professor of Pharmacology at the University of Bristol
Dr Carole Hunter	Lead pharmacist at the alcohol and drug recovery services at NHS Greater Glasgow and Clyde
Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham
Professor Tim Millar	Professor of Substance Use and Addiction Research Strategy Lead at the University of Manchester
Mr Rob Phipps	Former Head of Health Development Policy Branch, Department of Health, Social Services and Public Safety, Northern Ireland
Mr Harry Shapiro	Director – DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Paul Stokes	Senior Clinical Lecturer in mood disorders, King's College, London
Dr Ann Sullivan	Consultant physician in HIV and Sexual health

Professor Matthew Sutton	Chair in Health Economics at the University of Manchester and Professorial Research
Professor David Taylor	Professor of Psychopharmacology, King's College, London
Professor Simon Thomas	Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Dr Derek Tracy	Consultant Psychiatrist and Clinical Director, Oxleas NHS Foundation Trust
Miss Rosalie Weetman	Senior Commissioning Manager of Substance Misuse

Annex 10 – ACMD NPS Committee membership, at time of publication

Dr Kostas Agath	Consultant Psychiatrist (addictions), CGL Southwark
Mr Paul Bunt	Director of Casterton Event Solutions Ltd, Former Drug Strategy Manager for Avon and Somerset Constabulary
Dr Anne Campbell	Senior lecturer in social work and Co-Director of the drug and alcohol research network at Queens University Belfast
Mr John Corkery	Senior Lecturer in Pharmacy Practice at University of Hertfordshire
Mr Lawrence Gibbons	Head of Drug Threat – NCA Intelligence Directorate – Commodities
Dr Hillary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Professor Graeme Henderson	Professor of Pharmacology at the University of Bristol
Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham
Professor Fiona Measham	Professor and chair in criminology, University of Liverpool; co-founder and co-director, the Loop
Mr Harry Shapiro	Director - DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Ann Sullivan	Consultant physician in HIV and Sexual health
Professor Simon Thomas	NPS Committee Chair, Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Ric Treble	Retired Laboratory of the Government Chemist (LGC) expert
Dr Mike White	Former Forensic Intelligence Adviser
Dr David Wood	Consultant physician and clinical toxicologist at Guy's and St Thomas' and reader in clinical toxicology at

In addition to members of the NPS committee listed, significant contributions were made by NPSAD and the NPIS and a special mention would like to be extended to both organisations.

References

ACMD (2016a) Reducing Opioid-related Deaths.

ACMD (2016b). Diversion and Illicit Supply of Medicines.

Amlani A, McKee G, Khamis N, et al. (2015). Why the FUSS (Fentanyl Urine Screen Study)? A cross-sectional survey to characterize an emerging threat to people who use drugs in British Columbia, Canada. *Harm Reduction J* 2015;12:54. doi:10.1186/s12954-015-0088-4.

Ayres WA, Starsiak MJ, Sokolay P. The bogus drug: Three methyl & alpha methyl fentanyl sold as "China White". *J Psychoactive Drugs*. 1981 Jan-Mar;13(1):91-3.

Ball M, Broadhurst R & Trivedi H. 2019. How much fentanyl is available on the darknet?. *Statistical Bulletins* no. 18. Canberra: Australian Institute of Criminology. [Online resource, accessed 23/12/19: <https://aic.gov.au/publications/sb/sb18>]

Baldwin N, Gray R, Goel A, Wood E, Buxton JA, Rieb LM. Fentanyl and heroin contained in seized illicit drugs and overdose-related deaths in British Columbia, Canada: An observational analysis. *Drug Alcohol Depend*. 2018 Apr 1;185:322-327. doi: 10.1016/j.drugalcdep.2017.12.032. Epub 2018 Feb 20.

Belzak L, Halverson J. Evidence synthesis - The opioid crisis in Canada: a national perspective. *Health Promot Chronic Dis Prev Can*. 2018 Jun;38(6):224-233

Bijral P, Hayhurst KP, Bird SM, Millar T. Prevalence of recent fentanyl use among treated users of illicit opioids in England: based on piloted urine drug screens. *Clin Toxicol (Phila)*. 2019 May;57(5):368-371. doi: 10.1080/15563650.2018.1527927. Epub 2018 Dec 16

Blane GF, Boura ALA, Fitzgerald AE, Lister RE. (1967). Actions of etorphine hydrochloride (M99): a potent morphine-like agent. *Br J Pharmac Chemother* 1967; 30: 11-22

Boddiger D. Fentanyl-laced street drugs "kill hundreds". *Lancet* 2006; 368: 569-70

Bryson EO, Silverstein JH. Addiction and substance abuse in anesthesiology. *Anesthesiology*. 2008 Nov;109(5):905-17. doi: 10.1097/ALN.0b013e3181895bc1.

Cahill CM, Walwyn W, Taylor AMW, Pradhan AAA, Evans CJ. (2016). Allostatic mechanisms of opioid tolerance beyond desensitization and downregulation. *Trends Pharmacol Sci*. 2016 Nov;37(11):963-976. doi: 10.1016/j.tips.2016.08.002. Epub 2016 Sep 23.

Canadian Broadcasting Corporation (CBC). (2017). 'It makes me sick': fake fentanyl patches circulate in northern Ontario. [Online resource, accessed 23/12/19: <https://www.cbc.ca/news/canada/sudbury/fake-fentanyl-patch-northern-ontario-1.4272188>]

Carre, Z. & Ali, A. (2019) Finding a Needle in a Haystack: Take-Home Naloxone in England 2017/18, London: Release.

Centers for Disease Control and Prevention, CDC. (2017). Notes from the Field: Counterfeit Percocet–Related Overdose Cluster — Georgia, June 2017. Morbidity and Mortality Weekly Report. U.S. Department of Health & Human Services. [Online resource, accessed 23/12/19;

<https://www.cdc.gov/mmwr/volumes/66/wr/mm6641a6.htm>]

Centers for Disease Control and Prevention, CDC. (2018). Opioid overdose; Prescription Opioid data. U.S. Department of Health & Human Services. [Online resource, accessed 23/12/19;

https://www.cdc.gov/drugoverdose/data/prescribing.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdrugoverdose%2Fdata%2Foverdose.html]

Ciccarone D, Ondocsin J, Mars S. (2017). Heroin uncertainties: exploring users' perceptions of fentanyl adulterated and -substituted heroin. *Int J Drug Policy* 2017;46:146–155. doi: 10.1016/j.drugpo.2017.06.004.

Claridge H, Williams BD, Copeland CS. A deadly trend in fentanyl fatalities (England, 1998-2017). *Brit J Clin Pharmacol* 2019 (in press).

Concheiro et al., 'Postmortem toxicology of new synthetic opioids', *Frontiers Pharmacol*, 2018, Oct, 9, 1210.

Council on Foreign Relations (CFR) 2019. Mexico's drug war. [Online article, accessed 23/12/19; <https://www.cfr.org/backgrounder/mexicos-drug-war>]

Cowan, R. How the Narcs Created Crack: A War Against Ourselves. *National Review* 1986; 38: 26–34

Crown Prosecution Service, CPS (2019). Legal Guidance, Drug offences. [Online resources, accessed 23/12/2019 <https://www.cps.gov.uk/legal-guidance/drug-offences>]

Drug Enforcement Administration, DEA (2018a). The 2016 heroin signature program report. DEA intelligence report. DEA-DCW-DIR-035-018. Published October 2018 [accessed 23/12/2019; <https://www.dea.gov/sites/default/files/2018-10/Heroin%20Signature%20Report%20FINAL.pdf>]

Drug Enforcement Administration (2018b). Cocaine/fentanyl combination in Pennsylvania. DEA_PHL-BUL-061-18, February 2018.

Drug Enforcement Administration, Diversion Control Division (2017). Federal Register Volume 82, Number 249, pages 61700-61703, published 29 December 2017. [Online article, accessed 23/12/19; https://www.deadiversion.usdoj.gov/fed_regs/rules/2017/fr1229_4.htm]

Dunn M, Hill SL, Hardy G, Cooper J, Dargan PI, Wood DM, Grundlingh J, Parris R, Katariah H, Eddleston M, Officer J, Thomas SHL. Analytical prevalence of novel synthetic opioids including fentanyls in samples from patients presenting with apparent heroin overdose in the UK. *Clinical Toxicology* 2019; 57: p443.

Electronic Medicines Compendium (EMC) (2019a). *Fentanyl 50 microgram/ml Injection*. [accessed 23/12/19: <https://www.medicines.org.uk/emc/product/2852/smpc>]

Electronic Medicines Compendium (EMC) (2019b). *Nyxoid 1.8 mg nasal spray, solution in a single-dose container*. [accessed 23/12/19: <https://www.medicines.org.uk/emc/product/9292/smpc>]

Electronic Medicines Compendium (EMC) (2019c). *Prenoxad 1mg/ml Solution for Injection in a pre-filled syringe*. [accessed 23/12/19: <https://www.medicines.org.uk/emc/product/3054/smpc>]

EMCDDA (2018) Fentanils and synthetic cannabinoids: driving greater complexity into the drug situation. An update from the EU Early Warning System. June 2018.

EMCDDA (2019). European Drug Report 2019. EMCDDA, Lisbon, June 2019

EU Early Warning System Advisory (2018a). Fake medicines (Xanax and OxyContin tablets) containing fentanils — Sweden, November 2017–January 2018. EU-EWS-RCS-AD-2018-0001. 09 February 2018.

EU Early Warning System Advisory (2018b). Fake oxycodone tablets containing methoxyacetylfentanyl — Sweden, 2018. EU-EWS-RCS-AD-2018-0003. 04 May 2018.

EU Early Warning System Advisory Update (2018c). Death linked to fake oxycodone tablets containing methoxyacetylfentanyl — Denmark, March 2018. EU-EWS-RCS-AD-2018-0003-U1. 25 June 2018.

Fernando D. Fentanyl-laced heroin. *J Am Med Assoc*. 1991;265(22):2962

Fischer B, Pang M, Tyndall M. The opioid death crisis in Canada: crucial lessons for public health. *Lancet* 2018; DOI:[https://doi.org/10.1016/S2468-2667\(18\)30232-9](https://doi.org/10.1016/S2468-2667(18)30232-9)

Gill H, Kelly E, Henderson H. (2019). How the complex pharmacology of the fentanils contributes to their lethality. *Addiction* 2019 Mar 18. doi: 10.1111/add.14614.

Government of Canada (2019a). Special Advisory Committee on the Epidemic of Opioid Overdoses. National report: Opioid-related Harms in Canada Web-based Report. Ottawa: Public Health Agency of Canada; December 2019. [Online, accessed 23/12/2019; <https://web-based-report.health-infobase.canada.ca/substance-related-harms/opioids>]

Government of Canada (2019b). Federal actions on opioids. Web-based Report. [Online, accessed 23/12/2019; <https://www.canada.ca/content/dam/hc-sc/documents/services/substance-use/problematic-prescription-drug-use/opioids/responding-canada-opioid-crisis/federal-actions/federal-actions-overview.pdf>]

Higashikawa Y, Suzuli S. Studies on 1-(2-phenethyl)-4-(N-propionylanilino)piperidine (fentanyl) and its related compounds. VI. Structure-analgesic activity relationship for

fentanyl, methyl-substituted fentanyls and other analogues. *Forensic Toxicology* 2008; 26: 1-5

Hikin L, Smith PR, Ringland E, Hudson S, Morley SR. Multiple fatalities in the North of England associated with synthetic fentanyl analogue exposure: Detection and quantitation a case series from early 2017. *Forensic Sci Int* 2018; 282: 179-183

House Committee on Energy and Commerce, HCEC. (2019) Hearing on 'Oversight of Federal Efforts to Combat the Spread of Illicit Fentanyl'. July 2016. Oversight and Investigations (116th Congress), [Online notification, accessed 23/12/2019: <https://energycommerce.house.gov/committee-activity/hearings/hearing-on-oversight-of-federal-efforts-to-combat-the-spread-of-illicit>]

International Narcotics Control Board. (INCB) INCB: Scheduling of fentanyl precursors comes into force (October, 2017)

International Narcotics Control Board, INCB. (2019). New Substances under international control, online release. [Online notification, Accessed 23/12/2019: <http://www.incb.org/incb/en/narcotic-drugs/Yellowlist/new-substances-under-control.html>]

Information Services Division (ISD). (2018). National Naloxone Programme Scotland; Monitoring Report 2017/18. 27 November 2018. NHS National Services Scotland. Information Services Division (ISD).

Kinshella M. W., Gauthier T., Lysyshyn M. Rigidity, dyskinesia and other atypical overdose presentations observed at a supervised injection site, Vancouver, Canada. *Harm Reduct J* 2018; 15: 64. doi: 10.1186/s12954-018-0271-5

Lozier MJ, Boyd M, Stanley C, Ogilvie L, King E, Martin C, Lewis L. Acetyl Fentanyl, a Novel Fentanyl Analog, Causes 14 Overdose Deaths in Rhode Island, March-May 2013. *J Med Toxicol.* 2015; 11:208-17

Lucyk S, Nelson L. Consequences of unsafe prescribing of transdermal fentanyl. *CMAJ.* 2016 Jun 14;188(9):638-639

Lynn RR, Galinkin JL. Naloxone dosage for opioid reversal: current evidence and clinical implications. *Therapeutic Advances in Drug Safety* 2018 Jan;9(1):63-88. doi: 10.1177/2042098617744161.

Macmadu A, Carroll JJ, Hadland SE, et al. (2017). Prevalence and correlates of fentanyl-contaminated heroin exposure among young adults who use prescription opioids non-medically. *Addict Behav* 2017; 68:35–38. doi:10.1016/j.addbeh.2017.01.014.

Marquardt KA, Tharratt RS, Musallam NA. Fentanyl remaining in a transdermal system following three days of continuous use. *Ann Pharmacother.* 1995 Oct;29(10):969-71.

Mayer S, Boyd J, Collins A, Kennedy MC, Fairbairn N, McNeil R. Characterizing fentanyl-related overdoses and implications for overdose response: Findings from a

rapid ethnographic study in Vancouver, Canada. *Drug Alcohol Depend.* 2018 Dec 1;193:69-74. doi: 10.1016/j.drugalcdep.2018.09.006. Epub 2018 Oct 12.

McGowan CR, Harris M2, Platt L2, Hope V, Rhodes T. Fentanyl self-testing outside supervised injection settings to prevent opioid overdose: Do we know enough to promote it? *Int J Drug Policy.* 2018; 58:31-36.

Moss MJ, Warrick BJ, Nelson LS, McKay CA, Dubé PA, Gosselin S, Palmer RB, Stolbach AI. (2017). ACMT and AACT position statement: preventing occupational fentanyl and fentanyl analog exposure to emergency responders. *Clin Toxicol (Phila).* 2017 September. *Clinical Toxicology*, DOI: 10.1080/15563650.2017.1373782

Morales KB, Park JN, Glick JL, Rouhani S, Green TC, Sherman SG. Preference for drugs containing fentanyl from a cross-sectional survey of people who use illicit opioids in three United States cities. *Drug & Alcohol Dependence* 2019; 204: 107547

Muhuri P, Gfroerer J, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. (August), 2013. [May 25, 2017]. CBHSQ Data Review 2013.

National Crime Agency, NCA (2017). Recent deaths possibly linked to fentanyl. April 2017. [available 23/12/2019; <https://nationalcrimeagency.gov.uk/who-we-are/publications/7-recent-deaths-possibly-linked-to-fentanyl/file>]

National Institute for Health and Care Excellence, NICE. Key therapeutic Topic 21 (2017). Medicines optimisation in chronic pain. [Online article, accessed 23/12/2019; <https://www.nice.org.uk/advice/ktt21/chapter/Evidence-context#opioid-medicines-in-chronic-pain>]

National Institute on Drug Abuse, NIDA. Overdose death rates. January 2019. [Online article, accessed 23/12/2019; <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>]

National Records of Scotland, NRS (2019). Drug related deaths in Scotland in 2018. Published July 2019.

National Safety Council, NSC (2019). Vehicle Deaths Estimated at 40,000 for Third Straight Year. [Online article, accessed 23/12/2019; <https://www.nsc.org/road-safety/safety-topics/fatality-estimates>]

NHS Digital (2019). Prescription Cost Analysis - England, 2018 [PAS]. National Statistics. Published 28 March 2019. [Accessed 23/12/2019; <https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018>]

Nolan ML, Shamasunder S, Colon-Berezin C, Kunins HV, Paone D. Increased Presence of Fentanyl in Cocaine-Involved Fatal Overdoses: Implications for Prevention. *J Urban Health.* 2019 Feb;96(1):49-54. doi: 10.1007/s11524-018-00343-z.

Northern Ireland Statistics and Research Agency, NISRA. (2019). Drug Related and Drug Misuse Deaths 2007- 2017. Published March 2019.

Office of National Drug Control Policy, (ONDCP). (2019) 8 Finalists Announced in \$1.55M Challenge for New Solutions to Detect Opioids in International Mail. National Security & Defence. Statements & Releases, June 2019. [Accessed 23/12/2019: <https://www.whitehouse.gov/briefings-statements/8-finalists-announced-1-55m-challenge-new-solutions-detect-opioids-international-mail/>]

Office for National Statistics, ONS (2018). Deaths related to drug poisoning in England and Wales: 2017 registrations. Published August 2018.

Office for National Statistics, ONS (2019). Deaths related to drug poisoning in England and Wales: 2018 registrations. Published August 2019.

Peiper NC, Clarke SD1, Vincent LB, Ciccarone D, Kral AH, Zibbell JE. Fentanyl test strips as an opioid overdose prevention strategy: Findings from a syringe services program in the Southeastern United States. *Int J Drug Policy*. 2019; 63:122-128

Public Health England (PHE) (2017). Providing take-home naloxone for opioid overdose. July 2017.

Public Health England (PHE) (2018). Guidance for local areas on planning to deal with fentanyl or another potent opioid. Published May 2018. [Online resource, accessed 23/12/2009; <https://www.gov.uk/government/publications/fentanyl-preparing-for-a-future-threat/guidance-for-local-areas-on-planning-to-deal-with-fentanyl-or-another-potent-opioid>]

Public Health England (PHE) (2019). Dependence and withdrawal associated with some prescribed medicines: An evidence review. September 2019.

Riches JR, Read RW, Black RM, Cooper NJ, Timperley CM. Analysis of clothing and urine from Moscow theatre siege casualties reveals carfentanil and remifentanil use. *J Anal Toxicol*. 2012 Nov-Dec; 36(9):647-56. doi: 10.1093/jat/bks078. Epub 2012 Sep 20

Rogers JS, Rehrer SJ, Hoot NR. Acetylfentanyl: an emerging drug of abuse *J. Emerg. Med.*, 50 2016 Mar;50(3):433-6. doi: 10.1016/j.jemermed.2015.10.014.

Rojkiewicz M, Majchrzak M, Celinski R, Kus P, Sajewicz M. Identification and physicochemical characterization of 4-fluorobutyrfentanyl (1-((4-fluorophenyl)(1-phenethylpiperidin-4-yl)amino)butan-1-one, 4-FBF) in seized materials and post-mortem biological samples. *Drug Test. Anal.*, 9 (2017), pp. 405-414

Royal College of Anaesthetists, Faculty of Pain Medicine (RCAFP) / PHE (2019). Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. [Online resource, accessed 23/12/2009; <https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware>]

Sellers EM, Schuller R, Romach MK, Horbay GL. Relative abuse potential of opioid formulations in Canada: a structured field study. *J Opioid Manag*. 2006 Jul-Aug;2(4):219-27.

Sentencing Council (2019). Drug offences involving newer and less common drugs. [Accessed 23/12/2009; <https://www.sentencingcouncil.org.uk/offences/magistrates-court/item/drug-offences-involving-newer-and-less-common-drugs/>]

Synthesis of Fentanyl (2015). Rhodium site archive. Website hosted by Erowid. [Accessed 23/12/2009: <https://erowid.org/archive/rhodium/chemistry/fentanyl.html>]

Streisand J. B., Bailey P. L., LeMaire L., Ashburn M. A., Tarver S. D., Varvel J., *et al.* Fentanyl-induced rigidity and unconsciousness in human volunteers. Incidence, duration, and plasma concentrations. *Anesthesiology* 1993; 78: 629–634.

Torjesen I. Fentanyl misuse in the UK: will we see a surge in deaths? *BMJ* 2018; k1564 doi: 10.1136/bmj.k1564 (Published 9 April 2018)

Torralva PR, Janowsky A. Noradrenergic mechanisms in fentanyl-mediated rapid death explain failure of naloxone in the Opioid Crisis. *J Pharmacol Exp Ther.* November 2019. 371 (2) 453-475; DOI: <https://doi.org/10.1124/jpet.119.258566>

Trivedi M, Shaikh S, Gwinnut C. (2007). Pharmacology of opioids. Update in *Anaesthesia* 2007; 118-124.

Tupper KW, McCrae K, Garber I, Lysyshyn M, Wood E. Initial results of a drug checking pilot program to detect fentanyl adulteration in a Canadian setting. *Drug Alcohol Depend.* 2018 Sep 1; 190:242-245. doi: 10.1016/j.drugalcdep.2018.06.020.

United States – China Economic and Security Review Commission, (USCC). (2018). Issue brief: fentanyl flows from China: an update since 2017. Published November 26, 2018 [accessed 23/12/19; <https://www.uscc.gov/sites/default/files/Research/Fentanyl%20Flows%20from%20China.pdf>]

United States Sentencing Commission, USSC (2018). Sentencing Guidelines for United States Courts. United States Sentencing Commission. BAC2210-40. November 2018. [accessed 23/12/19; https://www.ussc.gov/sites/default/files/pdf/amendment-process/federal-register-notices/20180503_FR_Final-Amdts.PDF]

United Nations Office on Drugs and Crime, UNODC. (2017). Recommended methods for the Identification and analysis of fentanyl and its analogues in biological specimens. Laboratory and Scientific Section UNITED NATIONS OFFICE ON DRUGS AND CRIME Vienna. [Accessed 23/12/2019; https://www.unodc.org/documents/scientific/Recommended_methods_for_the_identification_and_analysis_of_Fentanyl.pdf]

Vankova M. E., Weinger M. B., Chen D. Y., Bronson J. B., Motis V., Koob G. F. (1996). Role of central mu, delta-1, and kappa-1 opioid receptors in opioid-induced muscle rigidity in the rat. *Anesthesiology* 1996; 85: 574–583.

Vardanyan & Hruby, 'Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications', *Future Med Chem*, 2014 Mar, 6(4), 385-412

Veterinary Medicines Directorate (VMD) (2010). Summary of Product Characteristics – Large Animal Immobilon Solution for Injection. Created 2010, revised 2014. AN: 00750/2014 [Document available online. Accessed 23/12/2019; https://www.vmd.defra.gov.uk/productinformationdatabase/SPC_Documents/SPC_109519.DOCX]

Van Bever WF, Niemegeers CJ, Schellekens KH, Janssen PA. (1976). N-4-Substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin. Drug Res 26: 1548–1551, 1976.

Volpe DA, McMahon Tobin GA, Mellon RD, Katki AG, Parker RJ, Colatsky T, Kropp TJ, Verbois SL. (2011). Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol. 2011; 59: 385-90

WEDINOS. Philtre bulletin Issue 12 (2017). [Accessed 23/12/2019; http://www.wedinos.org/resources/downloads/Philtre_Issue_12.pdf]

WHO. Management of substance abuse Information sheet on opioid overdose, August 2018. [Accessed 23/12/2019 https://www.who.int/substance_abuse/information-sheet/en/]

WHO. Carfentanil critical review report. Expert Committee on Drug Dependence Thirty-ninth Meeting Geneva, 6-10 November 2017 [accessed 23/12/2019; https://www.who.int/medicines/access/controlled-substances/Critical_Review_Carfentanil.pdf]