ACRYLOYLFENTANYL

Critical Review Report

Agenda Item 4.7

Expert Committee on Drug Dependence

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Contents

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Summary

First described in 1981, acryloylfentanyl is an analogue of fentanyl (a scheduled opioid in the 1961 Single Convention) that in the last few years has appeared on drug websites selling "research chemicals", predominantly in nasal spray solutions or powder form often as an alternative to illicit opioids. In non-clinical laboratory studies, it has been shown to be an opioid receptor agonist and a potent and long-lasting analgesic agent but has no known or recorded therapeutic use.

Acryloylfentanyl is being used and abused for non-medical purposes in the same setting and for the same desired effects as other opioids. Reported adverse effects (including intoxication) include miosis, decreased consciousness and respiratory depression. Fatalities have been reported in Europe and the United States, occurring within a relatively short time period.

The potency of the drug also poses health risks to those coming into contact with any material, which includes the general public as well as medical, forensic and law enforcement personnel. Whilst there are no animal or human studies that have investigated the abuse and dependence potential of acryloylfentanyl, the information available demonstrates acryloylfentanyl is liable to similar abuse and productive of similar ill effects as fentanyl and other fentanyl analogues.

1. Substance identification

A. International Nonproprietary Name (INN)

None

B. Chemical Abstract Service (CAS) Registry Number

82003-75-6 free amine
79279-03-1 hydrochloride salt

C. Other Chemical Names

N-(1-Phenethylpiperidin-4-yl)-*N*-phenylacrylamide
N-(1-phenethylpiperidin-4-yl)-*N*-acroylanilinopiperidine
N-(1-phenylethylpiperidin-4-yl)-*N*-phenylacrylamide
Acryloylfentanyl
Acrylfentanyl

D. Trade Names

None

E. Street Names

acryloyl-F, Acr-F, ACF [1,2]

F. Physical Appearance

Acryloylfentanyl hydrochloride is a white solid.[3]

G. WHO Review History

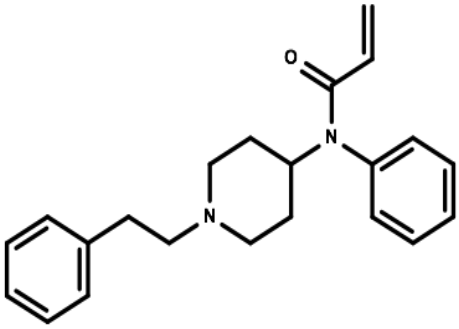
Acryloylfentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that acryloylfentanyl is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

A. Chemical Name

IUPAC Name:
N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide
CA Index Name:
N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl-2-propenamide

B. Chemical Structure



Free base:

Molecular Formula: $C_{22}H_{26}N_2O$
Molecular Weight: 334.46 Da

C. Stereoisomers

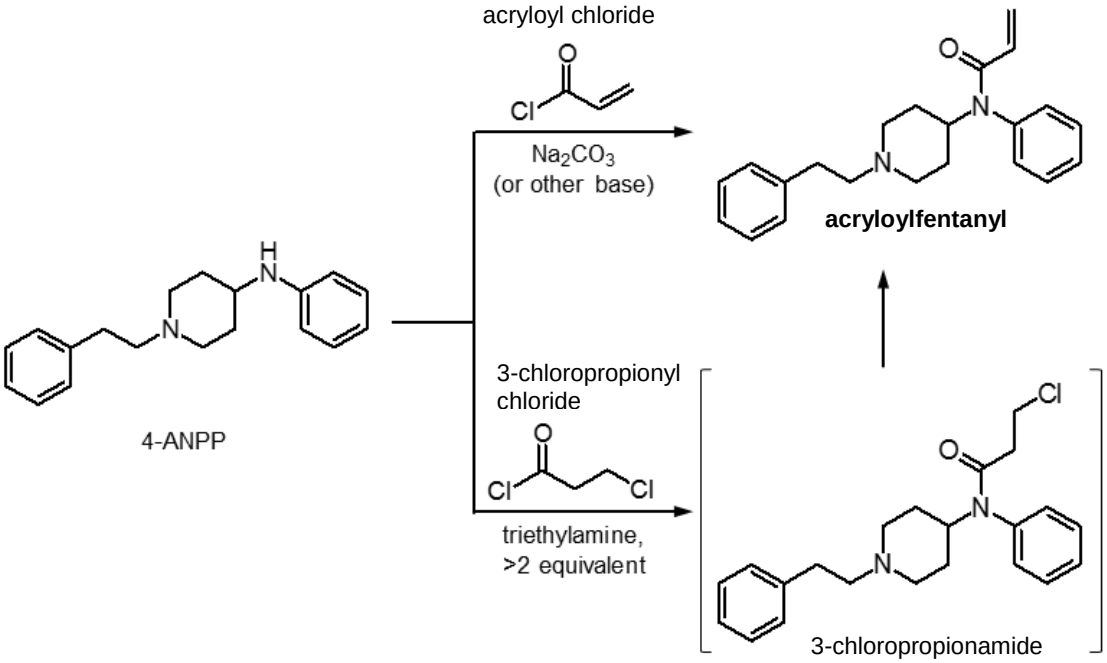
None

D. Methods and Ease of Illicit Manufacturing

The synthesis and activity of acryloylfentanyl was first described in 1981.[3] The synthesis of acryloylfentanyl utilises a similar multistep process to fentanyl but involves a different acylating agent in the final acylation step for acryloylfentanyl. The synthetic procedures for fentanyls are chemically straightforward, use common laboratory equipment and precursors, and detailed recipes are available on the Internet. Aside from the relative ease in manufacturing, the potency of acryloylfentanyl and other fentanyls poses a serious risk of dangerous exposure during its manufacture as well as presenting a serious risk of poisoning to law enforcement and forensic professionals coming in to contact with clandestine laboratories.

The two published synthetic methods of acryloylfentanyl describe the acylation of the common precursor 4-ANPP (*N*-phenyl-1-(2-phenylethyl)piperidin-4-amine) with acryloyl chloride or 3-chloropropionyl chloride.[3-6] Acylation of 4-ANPP with acryloyl chloride in the presence of a base, such as sodium carbonate, in an inert solvent directly produces acryloylfentanyl, without an intermediate (that is not isolated) with the 3-chloropropionyl chloride route. A substantial amount of trimethylamine and a minor amount of 4-ANPP was found in a seized sample of acryloylfentanyl powder suggesting the use of the latter method for that particular

preparation.[1,2,7] Other acylation methods that use an activated ester of acrylic acid can also be used. An alternative, potential synthetic route for the manufacture of acryloylfentanyl would involve the alkylation of *N*-phenyl-*N*-(piperidin-4-yl)acrylamide with a phenethyl halide in the presence of sodium (bi)carbonate or another base.[2]



E. Chemical Properties

Melting point:
hydrochloride (HCl) salt: 259–260°C[1]; 252–258°C with decomposition[4]; 191–194 °C[6]
free amine: 101–103 °C[6]

Boiling point: no data

Solubility: no data

F. Identification and Analysis

There is no information on the reaction of acryloylfentanyl to presumptive colour tests. Similar to fentanyl, it is expected that acryloylfentanyl does not give a positive response to immunoassay tests developed for morphine-type opioids. There are no data on whether immunoassays developed for fentanyl or other fentanyls would give positive responses to acryloylfentanyl.[1]

Gas chromatography-mass spectrometry (GC-MS)[6-8] and liquid chromatography-mass spectrometry (LC-MS) (the latter with and without high resolution mass-spectrometry) have been used for identification of acryloylfentanyl, including in biological fluid.[9,10] Infrared (IR) spectroscopy, proton/carbon nuclear magnetic resonance (NMR) spectroscopy and matrix-assisted laser desorption/ionization Orbitrap (MALDI/Orbitrap) mass spectrometric analyses have been used to identify acryloylfentanyl.[6-8] Furthermore, a recently developed capillary electrophoresis-electrospray-tandem mass spectrometry method for the trace level analysis of fentanyls could be applicable for acryloylfentanyl.[11]

The challenges associated with acryloylfentanyl analysis include some commonality in mass-spectral fragments with fentanyl and other fentanyls as well as low concentrations in biological fluid requiring sensitive techniques to be used.

3. Ease of Convertibility Into Controlled Substances

Acryloylfentanyl may serve as a precursor to the internationally controlled fentanyl (at least in theory) by saturating the double bond of the acrylamide moiety using catalytic hydrogenation (for a similar example, see Huckle et al.).[12]

4. General Pharmacology

Overall, acryloylfentanyl is a potent and long-lasting antinociceptive agent acting on the opioid system with activity blocked by the opioid antagonist naloxone. Based on observations during a mouse-study, acute toxicity appears to be similar to that of fentanyl. Acryloylfentanyl also shares metabolic pathways similar to fentanyl.

A. Routes of administration and dosage

Acryloylfentanyl can be administered orally as a powder (including in capsules), as tablets, or as a solution; it can also be administered intranasally or sublingually via a spray; inhaled by vaporising e-liquid solutions ('vaping'); inhaled by smoking or vaporising the 'free base'; injected; and, applied transdermally.[1,2]

Data reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) regarding acute intoxications suspected to involve acryloylfentanyl showed that intranasal administration (presumed nasal spray), was the most common route of administration (59%; 10 out of 17 non-fatal intoxications for which a route of administration was reported); while the most common physical form used were 'nasal solutions' (68%; 13 out of 19 cases for which a physical form was reported).[1] Less commonly, snorting of powder or crushed tablets, oral consumption of tablets, and injection of a 'nasal solution' were also reported.

Discussions on user websites include the descriptions of homemade preparations for vaping acryloylfentanyl in an "e-cigarette". In one case, a user describes the preparation of a 'homemade, rum-flavoured e-liquid prepared from 65% propylene glycol and 35% vegetable glycerol' to provide an 'acrylfent' solution of 24 mg/ml

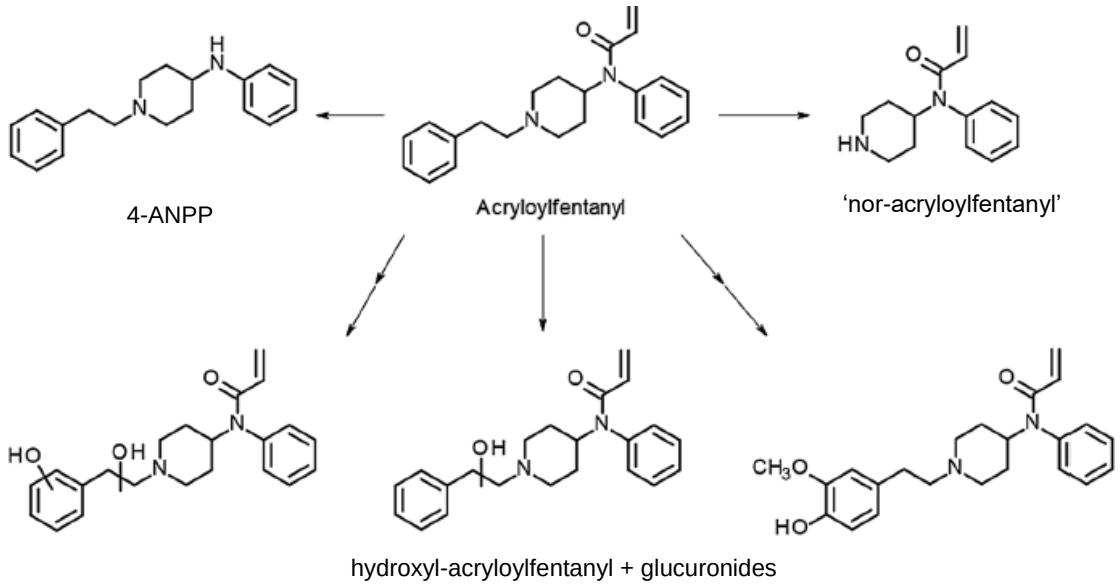
for vaping.[1] In addition, an experience with a homemade transdermal patch preparation has also been discussed on a user forum.[1]

In relation to dosage, limited information is available regarding the dose and the dose regimens of acryloylfentanyl. From the limited data available it is not possible to discern the 'typical' dosages administered by users. Whilst a range of doses have been reported, these appear to differ depending on factors such as the route of administration, the tolerance of the users, the use of other drugs, and the desired effects.[2] Given the difficulties of collecting such data accurately the information should be used with caution but data reported to the EMCDDA regarding acute intoxications suspected to involve acryloylfentanyl indicated that a range of doses may be used, with re-dosing during the course of a day reported in some cases.[1] This included two cases that reported use of '20 mg' intranasally per day in potentially tolerant individuals following use of the substance over the preceding months. Analysis of the concentration of acryloylfentanyl in nasal spray solutions from Sweden suggests that a 10 mL spray bottle typically contains 20 mg of the substance with metered sprays of 0.1 mL (0.2 mg) per actuation.[9]

Some additional information on dosage from user websites described for nasal sprays, doses of 0.0027 mg to 0.2 mg were reported on user websites.[1] Some of these reports suggested that oral doses of 5–12.5 μg of acryloylfentanyl may produce 'light' effects, and doses of 25–47.5 μg may produce 'strong' effects. Aside from the problem of interchangeable use of milligrams (mg) and micrograms (μg) in user forums it should be noted that the preparation of solutions containing milligram amounts of substance is inherently prone to risks in weighing and dilution and therefore solutions with higher (or lower) concentrations can be mistakenly prepared and/or sold.

B. Pharmacokinetics

Whilst there appears to be no preclinical or human clinical studies pertaining to the pharmacokinetics of acryloylfentanyl, the pharmacokinetics and the metabolic pathway of acryloylfentanyl are expected to be similar to those of fentanyl or acetylfentanyl.[13-19] Fourteen biotransformation products, including phase I and II metabolites were identified in a recent study of acryloylfentanyl metabolites produced by human hepatocytes *in vitro* and of those detected in the urine in five cases of death related to acryloylfentanyl - as identified following hydrolysis of glucuronidated and/or sulfated phase II conjugates.[10] Aside from 4-ANPP as a minor component, 'nor-acryloylfentanyl' and various hydroxyl-acryloylfentanyls were detected in addition to acryloylfentanyl itself in blood and urine.



Consequently, similar to fentanyl, the biotransformation of acryloylfentanyl involves oxidative N-dealkylation, presumably catalysed by cytochrome P450 (CYP450) enzymes, producing the biologically inactive desphenethyl metabolite, 'nor-acryloylfentanyl'.[10,14] Additional oxidative metabolic processes were monohydroxylations either on the alkyl chain of the phenylethyl moiety or on the piperidine ring as well as dihydroxylation of the aromatic ring of the phenylethyl moiety followed by O-monomethylation of the resulting catechol. Monophenols and diols, such as diphenol derivatives of the aniline moiety or a species dihydroxylated at the acryl moiety (not shown above), were also detected.[10] Amide hydrolysis (deacylation) forming 4-ANPP as a minor pathway is also similar to fentanyl. It should be noted though that due to incomplete acylation during manufacture, 4-ANPP could be present in the consumed products thus its detection in biological matrices might not be indicative of metabolism.[2]

C. Pharmacodynamics

In vitro studies: Recent Drug Enforcement Administration *in vitro* data have indicated that acryloylfentanyl selectively binds to the μ-opioid receptor with agonist functional activity.[20] Previously, Maryanoff et al. had determined the binding affinities of a series of compounds (including acryloylfentanyl) designed as potential covalent receptor affinity labels using a rat brain preparation and tritiated naloxone or naltrexone as competing opioid receptor ligands.[4] Morphine, fentanyl and the highly potent fentanyl analogue (+)-3-methylfentanyl were used as comparative standards. The IC_{50} values obtained for fentanyl and acryloylfentanyl were similar; morphine was somewhat less effective in inhibiting the binding of radiolabelled receptor antagonists.

Compound	IC_{50} (nM) [^{3}H]naloxone	IC_{50} [^{3}H]naltrexone
Morphine	4.2	27
Fentanyl	1.6	25
Acryloylfentanyl	1.4	17
(+)-3-methylfentanyl	0.6	1.3

The results of this study indicate that (at least in this particular rat brain preparation) the opioid receptor affinity of acryloylfentanyl is similar to that of fentanyl and somewhat higher than that of morphine. There was no evidence for irreversible binding of acryloylfentanyl to opioid receptors.

Separate bio-assay results did not show biological activity of acryloylfentanyl in assays that included a range of non-opioid related targets.[21]

Animal studies: There have been two studies investigating the antinociceptive activity of acryloylfentanyl in the mouse.[3,5-6] The first publication mentioning acryloylfentanyl describes an extensive structure–activity relationship study in mice involving 22 fentanyl analogues, with morphine and fentanyl as comparative standards.[3] Following intraperitoneal administration, the antinociceptive activity was assessed by the hot-plate test (55°C) measuring the latency of nociception.

Compound	ED_{50} (mg/kg)	Potency ratio to morphine	Potency ratio to fentanyl
Morphine	13.9	1	0.0045
Fentanyl	0.062	224	1
Acryloylfentanyl	0.082	169.5	0.76

It was found that in this mouse model of analgesia, acryloylfentanyl is about 170-times more potent as an antinociceptive agent than morphine, though somewhat less potent than fentanyl.

Using the hot-plate mouse assay, Essawi studied five fentanyl analogues, including acryloylfentanyl, as potential receptor affinity labels and antinociceptive agents with morphine and fentanyl as comparative standards.[5-6] Following intraperitoneal administration at doses below 1 mg/kg, acryloylfentanyl was found to be a more potent antinociceptive agent than fentanyl. While the effect of fentanyl at 0.1, 0.2 and 0.5 mg/kg dropped considerably at 60–70 minutes and became insignificant at 90–100 minutes after treatment, it was reported that at comparable doses, acryloylfentanyl maintained considerable analgesia at 90 and 120 minutes after administration. In its duration of action, the time-response profile of acryloylfentanyl resembled more closely that of morphine (20 mg/kg) than that of fentanyl. At 6.8 mg/kg and 17 mg/kg doses the antinociceptive effect of acryloylfentanyl was sustained up to 4.5 hours without signs of opioid toxicity. At the 25 mg/kg dose, it was reported that the motor activity was inhibited, but that the animals were not cataleptic and they returned to continuous circling behaviour 3.5 hours after treatment. However, following administration of a dose of 50 mg/kg, convulsions developed after 1 hour and 60% lethality was observed from apparent respiratory depression (an effect shared by fentanyl and other opioids). Pre-administration by 30 minutes of 2 mg/kg naloxone blocked the antinociceptive effect of 0.85 mg/kg acryloylfentanyl for about 40 minutes, after which this antagonist effect disappeared and analgesia and other morphine-like effects could be noted for about 50 minutes. A similar transient antagonist effect was observed when naloxone (2 mg/kg) was administered 40 minutes after acryloylfentanyl treatment (0.85 mg/kg): the reversal of the antinociceptive effect lasted for 70

minutes, and then antinociception returned to the same level as before naloxone administration.[2]

5. Toxicology

In the mouse study by Essawi involving the intraperitoneal injection of acryloylfentanyl, a dose of 25 mg/kg caused a transient suppression of motor activity; while, at a dose of 50 mg/kg the drug produced convulsions 1 hour after drug administration and 60% lethality was observed from apparent respiratory depression.[5-6] From these data, an acute mouse LD_{50} value between 25 and 50 mg/kg may apply for intraperitoneal administration.

No other acute or chronic pre-clinical studies were identified that have examined the toxicity of acryloylfentanyl in humans or animals.

Of separate consideration is that whilst acrylamide has been identified as a toxic substance and the acrylamide moiety of acryloylfentanyl could irreversibly modify or inactivate the opioid receptor protein, there is no evidence that this occurs with acryloylfentanyl.[22-23]

6. Adverse Reactions in Humans

Cases of Acryloylfentanyl Intoxication in Humans

Non-fatal Cases

In Sweden between March and August 2016, 21 acute intoxications associated with acryloylfentanyl were reported as part of the Swedish STRIDA project, with 11 being analytically confirmed.[9] 8 cases involved acryloylfentanyl as the only fentanyl, the 3 other cases involved acryloylfentanyl and 4-chloro-isobutyrfentanyl (1 case), 4-fluoro-isobutyrfentanyl (1 case), and tetrahydrofuran-fentanyl (1 case). Patients were aged between 19 and 51 years (median 28) and 91% were men. 6 patients (55%) were monitored at the emergency department, and five were admitted to intensive care. Decreased consciousness, respiratory depression and miosis were the typical clinical features. In 8 cases, the antidote naloxone was administered to counter the opioid effects with observed reversal of the poisoning reported in 4 of these cases. The 4-fluoro-isobutyrfentanyl patient was reported to have subsequently died of brain oedema. Where measured, the serum acryloylfentanyl concentration (n = 8) ranged between 0.5 and 2.1 (median 0.9) ng/mL, and in urine (n = 9) ranged between 0.2 and 10.5 (mean 4.6, median 5.2) μg/mmol creatinine. In the 3 cases where other fentanyls were detected, higher serum (5-45 ng/mL) and urine (11-136 μg/mmol creatinine) concentrations were found. Other new psychoactive substances (e.g. flunitrazolam) and/or other drugs were detected in 5 cases.

Fatal Cases

There have been 130 reported fatalities associated with acryloylfentanyl occurring in the USA (83 cases), Sweden (43), Estonia (3) and Denmark (1).

In the USA, the fatalities occurred from September 2016 and occurred in five states - Illinois (27), Maryland (22), New Jersey (1), Ohio (31) and Pennsylvania (2).[20]

In Europe, a total of 47 analytically confirmed deaths associated with acryloylfentanyl were reported.[1] Data were available in 44 deaths reported by Denmark and Sweden, occurring between April and December 2016, with 32 cases occurring between June and August 2016. Of these deaths, 38 were male (86%) and 6 were female (14%). The mean age of the male decedents was 31 years (median 29) and ranged from 19 to 54 years; the mean age of the female decedents was 42 years (median 43) and ranged from 29 to 50 years.[1,24] An assessment of the data for toxicological significance found that in essentially all deaths, acryloylfentanyl was either the cause of death or was likely to have contributed to death (even in presence of other substances) and in 2 of the deaths acryloylfentanyl was the sole drug present.[1,25] Acryloylfentanyl was quantified in all cases and post-mortem blood concentrations between 0.01 and 5.0 ng/g were recorded (mean 0.78; median: 0.19 ng/g) (somewhat but not exactly equivalent to μg/L). In terms of other drugs, a range of other substances were found, including: benzodiazepines, zopiclone, pregabalin and gabapentin (gabapentinoids), ethanol, cannabinoids (including synthetic cannabinoids), synthetic cathinones, amphetamines, antidepressants, antipsychotics. In terms of opioids, acryloylfentanyl was the sole opioid present in 38 of the 44 cases. In the remaining 6 cases, other opioids detected were buprenorphine (2 deaths), oxycodone (1); oxycodone and hydrocodone (1); oxycodone and 4-fluoro-isobutyrfentanyl (1); and, 4-chloro-isobutyrfentanyl (1). In a review of the data, it was stated that whilst other substances may have contributed to some toxicity in their own right, a synergistic effect with acryloylfentanyl would have been likely (e.g. other central nervous system depressants such as ethanol, benzodiazepines, 'z-drugs', gabapentinoids, and opioids, etc.).[1-2] It was also assessed that the pharmacological opioid nature of acryloylfentanyl meant the primary toxic contribution could have been attributed to the drug and death may not have occurred if acryloylfentanyl had not been used.[1-2]

As individuals were found dead or died in a home environment (their own or someone else's) in 32 of the deaths, information regarding symptoms prior to death were not available. However, in 3 cases the deceased was described as being unconscious prior to death, and in one of these cases it was reported that the deceased lost consciousness 10 minutes after using acryloylfentanyl. In a further case, the deceased was described as being found on the floor with a 'seizure disorder' and that attempts at resuscitation failed.[1,24]

7. Dependence Potential

A. Animal Studies

No studies were identified that have investigated the dependence potential of acryloylfentanyl in animal models.

B. Human Studies

No studies were identified that have investigated the dependence potential of acryloylfentanyl in humans. However, the limited information available from user websites suggests that some users of acryloylfentanyl report an urge to re-dose as well as symptoms suggestive of withdrawal.[1]

8. Abuse Potential

A. Animal Studies

No studies were identified that have investigated the abuse potential of acryloylfentanyl in animal models.

B. Human Studies

No studies were identified that have investigated the abuse potential of acryloylfentanyl in humans, however, analytically confirmed use and abuse of acryloylfentanyl has been reported.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

No evidence has been found that acryloylfentanyl has been therapeutically used.

10. Listing on the WHO Model List of Essential Medicines

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

11. Marketing Authorizations (as a Medicinal Product)

None.

12. Industrial Use

No evidence has been found that acryloylfentanyl has been or is used in industry.

13. Non-Medical Use, Abuse and Dependence

Overall, acryloylfentanyl use and abuse has currently been reported in: Denmark, Estonia, Finland, Latvia, Sweden and the USA.

Whilst no studies have investigated the prevalence of use of acryloylfentanyl in the general population in these countries, it has been considered that the available information does not suggest widespread use of the substance in the population and abuse is associated with those individuals abusing prescription opioid analgesics and heroin. It is also considered to be a drug of interest by some psychonauts (experimental drug users).[1,20]

In the USA, acryloylfentanyl was identified in a total of 110 drug exhibits submitted to forensic laboratories from May 2016.[20] These exhibits were encountered by law enforcement in 20 states. Further relevance of this is that accidental exposure of acryloylfentanyl and other fentanyls (through skin contact, inhalation, or ingestion) pose a serious risk of poisoning to law enforcement and forensic/laboratory personnel.[1,20]

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

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

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

In addition to users, as for law enforcement and forensic laboratory personnel, the potency of acryloylfentanyl and other fentanyls pose a serious risk of accidental exposure to products with the potential for subsequent poisoning of the public, emergency personnel, as well as medical/laboratory personnel.[1,20]

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

15. Licit Production, Consumption and International Trade

Not applicable. Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit Manufacture and Traffic and Related Information

Data from seizures, collected samples and acute intoxications in Europe suggests that the substance is sold online, typically as a powder and as ready-to-use nasal sprays.[1] Acryloylfentanyl is often described as a 'research chemical' on such websites, available in small and wholesale amounts. In 3 small seizures of acryloylfentanyl, the product also contained carfentanil and heroin (relative amounts not reported). Prior to March 2017, the available information suggested that acryloylfentanyl was produced by chemical companies based in China.[1] Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

Acryloylfentanyl is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

Acryloylfentanyl has been controlled in China since March 2017. It is also controlled in Canada and the USA (the latter as a temporary order July 2017).

Acryloylfentanyl is controlled in European Union Member States following a decision of the Council of the European Union in April 2017.

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

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None

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

Please refer to separate Annex 1 document published on ECDD website