



Critical Review Report: Methoxyacetyl Fentanyl

Expert Committee on Drug Dependence

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Contents

Acknowledgements.....	5
Summary.....	6
1. Substance identification	7
A. <i>International Nonproprietary Name (INN).....</i>	<i>7</i>
2-methoxy-N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl] acetamide.....	<i>7</i>
B. <i>Chemical Abstract Service (CAS) Registry Number.....</i>	<i>7</i>
C. <i>Other Chemical Names</i>	<i>7</i>
D. <i>Trade Names.....</i>	<i>7</i>
E. <i>Street Names.....</i>	<i>7</i>
F. <i>Physical Appearance.....</i>	<i>7</i>
G. <i>WHO Review History.....</i>	<i>8</i>
2. Chemistry.....	8
A. <i>Chemical Name.....</i>	<i>8</i>
B. <i>Chemical Structure.....</i>	<i>8</i>
C. <i>Stereoisomers.....</i>	<i>9</i>
D. <i>Methods and Ease of Illicit Manufacturing.....</i>	<i>9</i>
E. <i>Chemical Properties.....</i>	<i>10</i>
F. <i>Identification and Analysis.....</i>	<i>10</i>
3. Ease of Convertibility Into Controlled Substances.....	11
4. General Pharmacology.....	11
A. <i>Routes of administration and dosage.....</i>	<i>11</i>
B. <i>Pharmacokinetics.....</i>	<i>12</i>
C. <i>Pharmacodynamics.....</i>	<i>12</i>
5. Toxicology.....	13
6. Adverse Reactions in Humans.....	13
7. Dependence Potential.....	14
A. <i>Animal Studies.....</i>	<i>14</i>
B. <i>Human Studies.....</i>	<i>14</i>
8. Abuse Potential.....	15
A. <i>Animal Studies.....</i>	<i>15</i>
B. <i>Human Studies.....</i>	<i>15</i>
9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use	15
10. Listing on the WHO Model List of Essential Medicines	15
11. Marketing Authorizations (as a Medicinal Product).....	15
12. Industrial Use.....	16
13. Non-Medical Use, Abuse and Dependence.....	17

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence.....	18
15. Licit Production, Consumption and International Trade.....	18
16. Illicit Manufacture and Traffic and Related Information.....	19
17. Current International Controls and Their Impact.....	21
18. Current and Past National Controls.....	21
19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance.....	22
References	23

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Summary

As potent synthetic analogs of fentanyl continue to emerge on the illicit market, one of the more recent compounds appearing is methoxyacetyl fentanyl. Methoxyacetyl fentanyl belongs to the 4-anilidopiperidine class of synthetic opioids which is the same class of opioids as internationally controlled fentanyl and its derivatives. It appeared on the illicit market in 2017 for purchase as powders, liquids, and occasionally tablets. The few reports that are available examining the pharmacodynamics, patterns of use, toxicology, adverse events, or abuse liability of this compound indicate that methoxyacetyl fentanyl is an opioid with abuse liability and dependence potential similar to fentanyl, prescription opioids, and illicit opioids. The most serious acute health risk posed by methoxyacetyl fentanyl appears to be respiratory depression and death; reported overdose with methoxyacetyl fentanyl can be reversed with naloxone. The population likely to abuse methoxyacetyl fentanyl, either knowingly or unknowingly, intersects with the population using heroin, fentanyl, prescription opioid analgesics, and other fentanyl-related substances as evidenced by the routes of drug administration, the drug use history, and the paraphernalia found at fatal overdose cases. In summary, methoxyacetyl fentanyl is one of the latest fentanyl derivatives to be sold and used in a similar manner as other licit and illicit opioids. At the current time, there is evidence that methoxyacetyl fentanyl poses similar public health risks as the fentanyl derivatives that preceded it.

1. Substance identification

A. *International Nonproprietary Name (INN)*

2-methoxy-N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl] acetamide

B. *Chemical Abstract Service (CAS) Registry Number*

101345-67-9	base
101365-54-2	hydrochloride salt

C. *Other Chemical Names*

2-methoxy-N-(1-phenethylpiperidin-4-yl)-N-phenylacetamide
2-methoxy-N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]acetamide
2-methoxy-N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- acetamide
N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]-2- methoxyacetamide
N-[1-(2-phenylethyl)-4-piperidinyl]-2-methoxyacetanilide
methoxyacetylfentanyl
methoxyacetyl-F
methoxy-AcF

D. *Trade Names*

No trade names

E. *Street Names*

MAF
Methoxy
Synthetic heroin
Ching
desfluoro ofentaniil (Sweden)

F. *Physical Appearance*

White, off-white, or occasionally brown crystalline solid.

G. WHO Review History

Methoxyacetyl fentanyl has not been previously reviewed by WHO.

2. Chemistry

A. Chemical Name

IUPAC Name:

2-Methoxy-N-(1-phenethylpiperidin-4-yl)-N-phenylacetamide;

IUPAC International Chemical Identifier Key (InCHI Key):

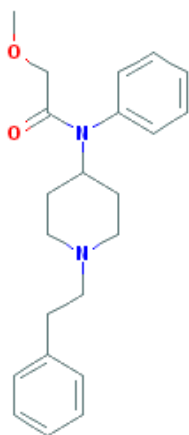
SADNVKRDSWWFTK-UHFFFAOYSA-N

CA Index Name:

Propanamide, N-(4-fluorophenyl)-2-methyl-N-[1-(2-phenylethyl)-4-piperidinyl]-

B. Chemical Structure

Free base:



Molecular Formula: $C_{22}H_{28}N_2O_2$; $C_{22}H_{28}N_2O_2 \cdot HCl$

Molecular Weight: 352.478 g/mol; 388.9 g/mol

C. Stereoisomers

No isomers.

D. Methods and Ease of Illicit Manufacturing

Methoxyacetyl fentanyl differs from fentanyl due to the presence of a 2-methoxyacetamide group in place of the propanamide group. Methoxyacetyl fentanyl is similar to ocfentanil due to the absence of a fluorine in the 2-position of the phenyl ring. Methoxyacetyl fentanyl differs from acetyl fentanyl by the addition of a methoxy group. Methoxyacetyl fentanyl synthesis has been described previously in the patent (Huang et al., 1985; Jilek et al., 1992) and scientific literatures (Jilek et al., 1990).

Two methods of synthesis using the precursor 4-anilino-N-phenethylpiperidine (ANPP) and 2-methoxyacetic anhydride (Jilek et al., 1990; Jilek et al., 1992) or using the pre-precursor N-phenethyl-4-piperidone (NPP) and aniline (Huang et al., 1985) are documented in the literature. Essentially, the manufacture of methoxyacetyl fentanyl uses precursors and synthetic methods similar to those used to manufacture the pharmaceutical fentanyl (Casy and Huckstep, 1988; Gupta et al., 2013; Zee and Wang, 1980). Therefore, the methods developed for the synthesis of fentanyl are also applicable to the synthesis of methoxyacetyl fentanyl. Use of a different acylating agent in the final acylation step, such as methoxyacetyl chloride would produce methoxyacetyl fentanyl. Using ANPP and methoxyacetyl chloride is a one-step process to make methoxyacetyl fentanyl. There is no information on the actual method(s) used for the production of particular batches of methoxyacetyl fentanyl that has been detected in Europe or the USA to date. Theoretically, most of the synthetic procedures that could be used would only require common laboratory equipment, a basic knowledge of synthetic chemistry, and the detailed recipes published or available on the internet to facilitate small-scale manufacturing by minor drug trafficking organizations.

E. Chemical Properties

Melting point

96-96°C (Jilek, 1990)

Boiling point

474.8±45.0 °C at 760 mmHg (predicted)

Solubility

Methoxyacetyl fentanyl contains a basic nitrogen atom in the piperidine ring which could readily form salts with inorganic and organic salts. The limited solubility data available on methoxyacetyl fentanyl or its hydrochloride or citrate salts indicates that it is soluble in dichloromethane, methanol, and water (Slovenian National Forensic Laboratories 2016, 2017). In addition, due to its similarity to fentanyl, the free base could be expected to be sparingly soluble in water; the hydrochloride and citrate salt could be expected to have greater aqueous solubility. As with fentanyl, methoxyacetyl fentanyl would be expected to be stable for at least 2 years; polymerization would not occur if properly stored.

F. Identification and Analysis

Although commonly used opioid drug screening methods including the enzyme-linked immunosorbent assay (ELISA) previously had difficulty differentiating between methoxyacetyl fentanyl and fentanyl due to the structural similarity between the two substances (Ruangyuttikarn, 1990; Alburges, 1992; US DEA, 2017a-3factor), a recently published comparison of Thermo DRI® Fentanyl Enzyme Immunoassay, the ARK™ Fentanyl Assay homogeneous enzyme immunoassay, and the Immunalysis® Fentanyl Urine SEFRIA™ Drug Screening Kit found the three assays showed overall good detectability (33%-95% cross-reactivity) for samples spiked with methoxyacetyl fentanyl (Helander et al., 2018). However, further confirmatory testing (i.e., mass spectrometry) is required to best identify methoxyacetyl fentanyl. Immunological assays developed for morphine-like

opioids would not be expected to give a positive response to methoxyacetyl fentanyl.

There is no information on the reaction of methoxyacetyl fentanyl to presumptive color tests.

Currently, high performance liquid chromatography time-of-flight (HPLC-TOF), gas chromatography-mass spectrometry (GC-MS), Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR), gas chromatography–mass spectrometry–infrared (GC-MS-IR) condensed phase, and nuclear magnetic resonance spectrometry (NMR) are available for the detection of methoxyacetyl fentanyl (Slovenian National Forensic Laboratory 2016, 2017). Recently, a method was developed using liquid chromatography tandem mass spectrometry for the quantitation of fentanyl, norfentanyl and 17 other fentanyl analogs including methoxyacetyl fentanyl (Fogarty et al., 2018)

A deuterated form, methoxyacetyl fentanyl-d5, is available for use as an internal standard for the quantification of methoxyacetyl fentanyl via GC- or LC-MS.

3. Ease of Convertibility Into Controlled Substances

At the time of the report, no information was found on whether methoxyacetyl fentanyl is converted into other controlled substances.

4. General Pharmacology

A. Routes of administration and dosage

Methoxyacetyl fentanyl has been seized as a liquid, in powder form, and occasionally as tablets. Based on forensic reports and paraphernalia found at overdose sites, routes of administration appear to be intravenous, as a nasal spray, and occasionally oral (EMCDDA-Europol, 2018; USA DEA, 2017a, USA DEA, 2017b).

B. Pharmacokinetics

Methoxyacetyl fentanyl is expected to be lipophilic; however no pharmacokinetic studies have been performed at the time of this report.

C. Pharmacodynamics

In radioligand binding assays, K_i values for methoxyacetyl fentanyl were: 0.560 ± 0.081 nM for MOR using [3H]DAMGO; 907 ± 74 nM for KOR using [3H]U69,593; and $1,530 \pm 110$ nM for DOR using [3H]DPDPE. Therefore, methoxyacetyl fentanyl selectively bound to μ -opioid receptors when [3H]-DAMGO was used as the radioligand (USA DEA, 2017c).

When methoxyacetyl fentanyl was evaluated in a [³⁵S]GTP γ S functional assay using preparations of transfected Chinese hamster ovary cells expressing human δ - and κ -opioid receptors and rat μ -opioid receptors, methoxyacetyl fentanyl produced $12.1 \pm 1.5\%$, $30.9 \pm 2.1\%$, and 71.2 ± 5.2 maximum stimulation with EC_{50} potencies of $1,390 \pm 460$ nM, $1,460 \pm 470$ nM, and 51.9 ± 4.7 nM, respectively. In summary, methoxyacetyl fentanyl was slightly less efficacious than fentanyl and morphine at rat μ -opioid receptors in the [³⁵S]GTP γ S functional assay receptors (USA DEA, 2017c).

Methoxyacetyl fentanyl, fentanyl, and morphine administered s.c. to CD1 mice produced dose-dependent increases in tail-flick latency in a 55°C tail withdrawal assay with ED_{50} values of 0.513 mg/kg, 0.115 mg/kg, and 12.68 mg/kg, respectively, until a maximal effect was obtained for each substance. A dose of 10 mg/kg naltrexone, s.c., shifted each the dose-response curves for methoxyacetyl fentanyl, fentanyl, and morphine to the right. Therefore, similar to fentanyl and morphine, methoxyacetyl fentanyl produced full antinociception and functioned as a μ opioid receptor agonist in vivo (USA DEA 2018a).

5. Toxicology

At the time of the report, there were no acute or chronic preclinical toxicology studies found.

6. Adverse Reactions in Humans

Similar to other opioids, the most serious acute health risk from using methoxyacetyl fentanyl is respiratory depression, which in overdose could lead to respiratory arrest, and death ((EMCDDA-Europol, 2018; Pattinson, 2008; White and Irvine, 1999). The antidote naloxone should reverse acute poisoning caused by methoxyacetyl fentanyl (Kim and Nelson, 2015; Ujváry *et al.*, 2017). The risk may be increased due to a lack of experience with effects and dosing for this particular novel opioid, the concurrent use of other central nervous system depressants such as other opioids, benzodiazepines, gabapentanoids, and alcohol, a lack of tolerance to opioids, and using the substance alone (such as at home) which would make it more difficult for users to call for help in the case of overdose.

To date, Sweden has reported 6 deaths with confirmed exposure to methoxyacetyl fentanyl occurring between December 2016 and June 2017. In these cases, methoxyacetyl fentanyl was the cause of death or contributed to the death as additional drugs were detected including other opioids in one case. Most of the individuals were found deceased in their homes; 5 were male aged between 28 and 41 years and 1 was female aged 28 years. The other substances detected in the deaths included other central nervous system depressants and other opioids in one of these cases (EMCDDA-Europol, 2018). In Denmark, methoxyacetyl fentanyl was either deemed the cause or a major contributing factor in the deaths of three individuals as revealed by the analyses detecting postmortem methoxyacetyl fentanyl and methoxyacetyl fentanyl metabolites (Mardel *et al.*, 2018).

Reports collected by the United States DEA indicate that methoxyacetyl fentanyl is being abused for its opioid properties and this use resulted in mortality. Authorities reported that a number of overdose deaths involving methoxyacetyl fentanyl were confirmed by post-mortem toxicology and medical examiner reports and occurred in North Carolina (15), Maryland (8), Pennsylvania (2), and New Jersey (1) in 2017. In most of these cases, other opioids such as fentanyl, despropionyl fentanyl, U-47700, cyclopropyl fentanyl, furanyl fentanyl, tetrahydrofuranyl fentanyl, and fluoroisobutyryl fentanyl were also detected. The DEA states that it is likely that the prevalence of the methoxyacetyl fentanyl in opioid-related emergency room admissions and deaths is underreported as standard immunoassays may not differentiate methoxyacetyl fentanyl from fentanyl (US-DEA, 2017a,b).

In addition to the adverse effects related to respiratory depression, material safety sheets from online chemical companies (for example, Cayman Chemical, Ann Arbor, MI USA), report that methoxyacetyl fentanyl may be irritating to the mucous membranes and upper respiratory tract and caution should be taken when handling. Methoxyacetyl fentanyl may be harmful if inhaled, ingested, or absorbed through the skin to cause eye, skin, or respiratory system irritation.

7. Dependence Potential

A. *Animal Studies*

At the time of the report, there are no physical dependence studies available.

B. *Human Studies*

From the limited data that exist from adverse effects reports in humans, dependence potential for methoxyacetyl fentanyl is likely high as methoxyacetyl fentanyl is a μ -opioid receptor agonist that shares some similarities with opioid analgesics such as morphine, fentanyl, and heroin.

8. Abuse Potential

A. Animal Studies

In rats trained to discriminate 3.2 mg/kg morphine, s.c., from saline, s.c., in a two lever drug discrimination assay, methoxyacetyl fentanyl, s.c., and fentanyl, s.c., fully substituted for morphine and all three compounds produced rate-decreasing effects after subcutaneous injections. The ED₅₀ values (+ 95% confidence limits) for each compound were calculated as follows: morphine [1.7 mg/kg (1.3 to 2.0)]; fentanyl [0.0093 mg/kg (0.0013 to 0.015)]; and 2-methoxyacetyl fentanyl [0.038 mg/kg (0.018 to 0.054)]. A dose of 0.03 mg/kg naltrexone, s.c., blocked the discriminative and rate-decreasing effects of methoxyacetyl fentanyl, fentanyl, and morphine (US DEA, 2018b; personal communication).

B. Human Studies

At the time of the report, no human abuse potential studies are available.

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

There is currently no therapeutic applications or recorded medical use at this time.

10. Listing on the WHO Model List of Essential Medicines

Methoxyacetyl fentanyl is not listed on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

To date, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, and Sweden reported that methoxyacetyl fentanyl: 1) has not been granted a marketing authorization as a medicinal product for human use; 2) has not been the subject of an application for marketing authorization as a medicinal product for human use; or, 3) has not had a case of suspended marketing authorization as a human medicine.

In addition, Austria, Belgium, Croatia, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom reported that methoxyacetyl fentanyl: 1) has not been granted a marketing authorization as a veterinary medicinal product; 2) has not been not the subject of an application for a marketing authorization as a veterinary medicinal product for use; or 3) has not had a case of suspended marketing authorization as a veterinary medicine.

Finally, the European Medicines Agency reported that methoxyacetyl fentanyl has not been granted a marketing authorization, been the subject of a suspended marketing authorization, or been the subject of a marketing authorization as a medicinal product for either human nor veterinary use through the centralized procedure. The EMA reports that to date, the only reported use of methoxyacetyl fentanyl is as an analytical reference material for scientific research (EMCDDA-Europol, 2018).

There are currently no investigational new drug applications or approved new drug applications for methoxyacetyl fentanyl based on a review by the United States Food and Drug Administration. Taken together from the available information, methoxyacetyl fentanyl does not appear to be used in the manufacture of a medicinal product in the European Union or the United States. There is a 'Nasal Drug Product and Methods of their Use' patent for opioid antagonist delivery in which methoxyacetyl fentanyl is specifically mentioned as a potential opioid that would cause overdose and the potential need for this delivery system (Keegan et al., March 16, 2017; US Patent Application US 20170071851A1). However, the data collection is incomplete and some countries indicated that this information is not known.

12. Industrial Use

No potential industrial use was detected for methoxyacetyl fentanyl besides as an analytical reference standard for scientific research and forensic applications. Methoxyacetyl fentanyl-d5 is also available for use as an internal standard for the

quantification of methoxyacetyl fentanyl using GC- or LC-MS methods for research and forensic purposes. For these purposes, methoxyacetyl fentanyl currently is available for purchase synthesized by various chemical companies.

13. Non-Medical Use, Abuse and Dependence

In different countries in Europe and North America between 2012 and 2018, multiple fentanyl analogues were reported to the UNODC early warning advisory on new psychoactive substances. These synthetic opioids are most commonly sold as adulterated/substituted heroin, liquids for nasal spray, or counterfeit prescription pills. In 2016, a record number of people died from a drug overdose in the United States, largely due to a rise in deaths associated with fentanyl and fentanyl analogues. Canada is also affected, with a large number of overdose deaths involving fentanyl and its analogues in 2016 (UNODC, World Drug Report 2018). Methoxyacetyl fentanyl is currently sold online and through illicit markets as a nonscheduled substitute for illicit opioids and/or prescription opioids. On drug forums, users report using the novel fentanyl-like derivatives for exploration of new opioid experiences, self-medication, such as the alleviation of pain, and/or to prevent opioid withdrawal (Zawilska, 2017). Novel psychoactive fentanyl analogs have appeared on the illicit market since 2013 with typical turnover times of 0.5–1 year (Helander and Backberg, 2017).

Users may include high-risk drug users as well as others (such as psychonauts) who may be experimenting with the substance. The population likely to abuse methoxyacetyl fentanyl would be assumed to overlap with the population abusing prescription opioid analgesics, heroin, fentanyl, and other fentanyl-related substances (Zawilska, 2017). This statement is supported by the routes of drug administration and drug use history documented in methoxyacetyl fentanyl overdose cases.

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

It is likely the abuse of methoxyacetyl fentanyl is as a replacement for heroin or other synthetic opioids, either known or unknown, as methoxyacetyl fentanyl seizures are predominantly powder form contained within glassine bags or in liquid form for nasal spray. Methoxyacetyl fentanyl has been encountered as a single substance or in a mixture with other opioids such as heroin, fentanyl, furanyl fentanyl, U-47700, cyclopropyl fentanyl, fluoroisobutyryl fentanyl, tetrahydrofuran fentanyl, despropionyl fentanyl. Methoxyacetyl fentanyl has been connected to fatal overdoses in which intravenous and insufflation routes of administration are authenticated. In individuals who may initiate or use a drug for the first time, methoxyacetyl fentanyl use is likely to be at risk for overdose, and death similar to that of other opioid analgesics (e.g., fentanyl, morphine, etc.). Methoxyacetyl fentanyl is available in liquid form which could be used as a nasal spray or e-liquid for vaping, formulations which may make it more acceptable to use (Zawilska, 2017). Similar to other fentanyls, accidental exposure to methoxyacetyl fentanyl may also pose a risk of severe poisoning. Those at risk may include law enforcement and emergency personnel, medical and forensic laboratory personnel, postal workers and the friends and family of users (EMCDDA-Europol, 2018; USA DEA, 2017a). If possible, these risks should be assessed and mitigated by appropriate training and protective measures such as training in resuscitation and adequate use of naloxone (Kim and Nelson, 2015; Ujváry *et al.*, 2017).

The chronic health risks for methoxyacetyl fentanyl likely share similarities to opioids such as heroin and other fentanyls including the potential for dependence.

15. Licit Production, Consumption and International Trade

There is currently no licit production, consumption, or trade for methoxyacetyl fentanyl.

16. Illicit Manufacture and Traffic and Related Information

Methoxyacetyl fentanyl can be found in trace amounts in illicitly manufactured material or mixed with heroin or other opioids making the detection very challenging for forensic laboratories and likely lead to the underreporting of the extent to which it appears on the market. Europol received reports from Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Slovenia, Spain, and Canada. Limited information was provided in relation to production, level of distribution, or trafficking. Sweden reported the vendors are purchasing methoxyacetyl fentanyl in China and mixing with water in nasal spray bottles but no know production is noted in Sweden. Methoxyacetyl fentanyl is ordered from a Swedish website and sent directly to the user. Finland reported the level of distribution and seizures to be minimal at the time of the EMCDDA-Europol Joint Report. In Slovenia, a case was reported in which methoxyacetyl fentanyl was purchased online and labelled as CHING (EMCDDA-Europol, 2018).

In total, the EMCDDA received 33 reports of seizures of methoxyacetyl fentanyl from Sweden (20), Latvia (7), Belgium (1), Denmark (1), Hungary (1), Slovenia (1), and the United Kingdom (1) by police or customs agencies between July and October 2017. Thirteen seizures consisting of 65.3 g of methoxyacetyl fentanyl powders were reported by Belgium, Denmark, Hungary, Latvia, Sweden, Slovenia, and the United Kingdom. Eighteen seizures consisting of 271 mL of liquid containing methoxyacetyl fentanyl were reported by Latvia, Sweden, and Norway. In two seizures in Sweden, ~75 tablets containing methoxyacetyl fentanyl were reported. For most of the seizures, there is no information on whether additional substances were also detected and no information on purity was shared. One confirmed seizure of 10 g methoxyacetyl fentanyl from China was reported by Canada to EMCDDA.

Austria, France, Slovenia, and the United Kingdom reported collecting four samples of methoxyacetyl fentanyl powder on the internet. In three instances, the

methoxyacetyl fentanyl was purchased as other substances and in the fourth instance, the user wished to purchase 4-HO-MET (4-Hydroxy-N-methyl-N-ethyltryptamine) and received a powder of both 4-HO-MET and methoxyacetyl fentanyl.

The commercial, web-based laboratory information management system STARLiMS used by the United States DEA registered 62 drug exhibits beginning in February 2017 containing methoxyacetyl fentanyl from California, District of Columbia, Florida, Georgia, Idaho, Maryland, North Carolina, New York, Rhode Island, South Carolina, Tennessee, Vermont, and West Virginia. Two registered drug exhibits were analyzed from June 2017 containing ~28 g methoxyacetyl fentanyl and acryl fentanyl from South Carolina and ~1.6 g of methoxyacetyl fentanyl from Idaho. The first US laboratory submissions of methoxyacetyl fentanyl were collected in February 2017 according to STARLiMS. At the time of this report, The National Forensic Laboratory Information System (NFLIS) registered 265 reports of methoxyacetyl fentanyl in 2017 from state forensic laboratories with Ohio reporting 123 cases and the remainder of reports from Georgia (9), Iowa (23), Massachusetts (18), Maryland (11), Minnesota (2), Missouri (1), Oregon (1), Pennsylvania (36), South Carolina (5), Tennessee (25), Utah (1), and Virginia (10). The DEA is not aware of any laboratory identifications methoxyacetyl fentanyl prior to 2016. Together, STARLiMS and NFLIS recorded 327 drug reports in which methoxyacetyl fentanyl was identified in drug exhibits submitted to forensic laboratories in 2017 from law enforcement encounters in many states in the USA.

The identification of methoxyacetyl fentanyl in one foil bag containing 7 g and one plastic bag containing 0.28 g, submitted in April 2017 as drug evidence, was reported to DEA from a local laboratory in Ohio. The DEA is not aware of any laboratory identifications of methoxyacetyl fentanyl prior to April 2017.

The DEA collected post-mortem toxicology and medical examiner reports on two confirmed fatalities associated with methoxyacetyl fentanyl which occurred in

Maryland (8), Pennsylvania (2), North Carolina (15), and New Jersey (1). It is likely that the prevalence of these substances in opioid related emergency room admissions and deaths is underreported as standard immunoassays may not differentiate fentanyl analogues from fentanyl.

17. Current International Controls and Their Impact

Two possible precursors of fentanyl and potentially methoxyacetyl fentanyl, 4-aminophenyl-1-phenethylpiperidine (4-ANPP) and N-phenethyl-4-piperidone (NPP, a pre-precursor) have been scheduled under the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.

18. Current and Past National Controls

The USA DEA temporarily placed methoxyacetyl fentanyl into Schedule I with two other fentanyl compounds, ortho-fluorofentanyl and tetrahydrofuranlyl fentanyl on October 26, 2017, citing high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. This temporary scheduling includes the isomers, esters, ethers, salts and salts of isomers, esters and ethers of methoxyacetyl fentanyl (US-DEA, 2017b).

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol added methoxyacetyl fentanyl to the list of new psychoactive substances to be monitored through the European Union Early Warning System and a profile of the substance was created on the European Database on New Drugs (EDND). Analytical details and other information, including a public health alert, have been exchanged between the EMCDDA, Europol, and the Member States, Turkey, and Norway and the European Commission and the EMA continue to be updated as needed.

Estonia, Finland, France, Ireland, Latvia, Lithuania, Sweden, the United Kingdom, and Norway reported that methoxyacetyl fentanyl is controlled under drug control

legislation. Austria, Belgium, Germany, Hungary, and Poland reported that methoxyacetyl fentanyl is controlled under specific new psychoactive substances control legislation. Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Greece, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, Spain, and Turkey reported that methoxyacetyl fentanyl is not subject to control measures at the national level. The EMCDDA and Europol continues to monitor methoxyacetyl fentanyl to confirm that new information is provided to the Member States, the European Medicines Agency, and the Commission through information exchange of the European Union Early Warning System.

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

Because abusers of NPS such as methoxyacetyl fentanyl are likely to obtain these substances through unregulated sources and from uncontrolled clandestine laboratories, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the end user (Baron et al., 2011; Davies et al., 2010). Limited pharmacological information is available for methoxyacetyl fentanyl, increasing the risk for harmful adverse events.

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