Tetrahydrofuranyl fentanyl (THF-F)

Critical Review Report

Agenda Item 4.10

Expert Committee on Drug Dependence

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Contents

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Summary

Unclassified and potent synthetic analogs of fentanyl continue to emerge on the illicit market, one of the latest agents appearing is tetrahydrofuranyl fentanyl (THF-F). Tetrahydrofuranyl fentanyl belongs to the 4-anilidopiperidine class of synthetic opioids which is the same class of opioids as internationally controlled fentanyl and its derivatives. Tetrahydrofuranyl fentanyl seems to have arrived on the scene shortly after the scheduling of other fentanyl derivatives in 2016 and is available for purchase as powders, tablets, or nasal spray solutions. No current studies are available examining the pharmacokinetics, pharmacodynamics, or abuse liability in animals although studies are presently underway sponsored by the U.S. DEA at the time of this report. However, the data collected so far from *in vitro* studies and the toxicological findings, and patterns of use indicate that tetrahydrofuranyl fentanyl is likely an opioid narcotic analgesic in humans with abuse liability and dependence potential similar to fentanyl and other illicit opioids.

The most serious acute health risk posed by tetrahydrofuranyl fentanyl appears to be respiratory depression and death; reported overdose with tetrahydrofuranyl fentanyl can be reversed with naloxone. The population likely to abuse tetrahydrofuranyl 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, tetrahydrofuranyl 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 tetrahydrofuranyl fentanyl poses similar public health risks as the fentanyl derivatives that preceded it.

1. Substance identification

A. International Nonproprietary Name (INN)

No INN at the time of the report.

B. Chemical Abstract Service (CAS) Registry Number

No CAS registry entry at the time of the report.

C. Other Chemical Names

N-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]tetrahydrofuran-2-carboxamide;
N-(1-phenethylpiperidin-4-yl)-N-phenyltetrahydrofuran-2-carboxamide;
N-fenyl-*N*-[1-(2-fenyletyl)piperidin-4-yl]tetrahydrofuran-2-karboxamid (Swedish);
tetrahydrofuranfentanyl;
tetrahydrofuran fentanyl;
tetrahydrofuranyl fentanyl;
tetrahydrofuran-fentanyl;

D. Trade Names

No trade names.

E. Street Names

THF-F; THF-fentanyl; tetrahydrofuran-F; Tetra

F. Physical Appearance

White, crystalline solid.

G. WHO Review History

Tetrahydrofuranyl fentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that THF-F 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.

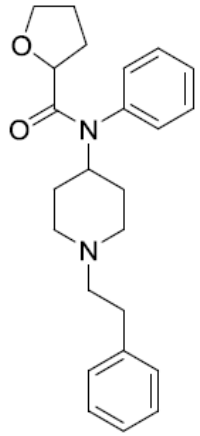
2. Chemistry

A. Chemical Name

IUPAC Name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] tetrahydrofuran-2-carboxamide
InCHI Key: OHJNHKUFSKAANI-UHFFFAOYSA-N
CA Index Name: Currently not indexed at the time of the report.

B. Chemical Structure

Free base:



tetrahydrofuranyl fentanyl

Molecular Formula: $C_{24}H_{30}N_2O_2$ (base) $C_{24}H_{30}N_2O_2 \bullet HCl$
Molecular Weight: 378.51 (base); 414.97 (HCl)

C. Stereoisomers

Tetrahydrofuranyl fentanyl has one positional isomer, which is 3-tetrahydrofuranyl fentanyl where the carboxamide is attached to the 3-position of the furan ring. Tetrahydrofuranyl fentanyl contains a stereogenic center allowing for the existence of a pair of enantiomers, (*S*)-tetrahydrofuranyl fentanyl and (*R*)-tetrahydrofuranyl fentanyl. There is no information on the actual enantiomers found on the illicit drug market at the time of the report.

D. *Methods and Ease of Illicit Manufacturing*

The synthesis of tetrahydrofuranyl fentanyl has not been described in the literature. However, the manufacture of tetrahydrofuranyl 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). The non-pharmaceutical fentanyl recently seized has been synthesized using the so-called "Siegfried route," which was first described in the 1980s, is relatively easy to perform, and readily available on the internet (see, for example, http://opioids.com/fentanyl/synthesis.html). Precursor chemicals used in this route are N-phenethyl-4-piperidone (NPP) or its derivative, 4-anilino-N-phenethylpiperidine (ANPP) (UNODC World Report, 2017).

Tetrahydrofuranyl fentanyl differs from fentanyl due to the presence of a tetrahydrofuran ring in place of an ethyl group attached to the carbonyl. Tetrahydrofuranyl fentanyl is closely related to furanyl fentanyl but differs by bearing a fully saturated furanyl ring (tetrahydrofuran) instead of an unsaturated ring (furan). Therefore, tetrahydrofuranyl fentanyl is the reduced analogue of furanyl fentanyl. To make tetrahydrofuranyl fentanyl, a different acylating agent is used in the final acylation step, such as tetrahydrofuranoyl chloride. A one-step

method uses N-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) and tetrahydrofuranoyl chloride. Tetrahydrofuranyl fentanyl contains one basic nitrogen atom in the piperidine ring which can readily form salts with organic or inorganic acids (EMCDDA-Europol, 2017; USA DEA, 2017a).

In summary, while the synthesis of tetrahydrofuranyl fentanyl has not been described in the literature, other routes developed for the production of fentanyl may also be used for the manufacture of tetrahydrofuranyl fentanyl. 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 available on the internet to facilitate small-scale manufacturing by minor drug trafficking organizations.

E. Chemical Properties

Melting point: Unknown at the time of the report.

Boiling point: Unknown at the time of the report.

Solubility: There are no solubility data on tetrahydrofuranyl fentanyl or its hydrochloride salt at the time of this report. However, 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, tetrahydrofuranyl fentanyl would be expected to be stable for at least 2 years; polymerization will not occur if properly stored.

F. Identification and Analysis

At the current time, commonly used opioid drug screening methods including the enzyme-linked immunosorbent assay (ELISA) are unable to differentiate between tetrahydrofuranyl fentanyl and fentanyl due to the structural similarity between the two substances (US DEA, 2016). Similarly, tetrahydrofuranyl fentanyl is not expected to give a positive response to tests developed for morphine-type opioids. There is no information on the reaction of tetrahydrofuranyl fentanyl to presumptive color tests.

To positively identify tetrahydrofuranyl fentanyl, additional testing is required including nuclear magnetic resonance, gas chromatography – mass spectrometry (GC-MS), high performance liquid chromatography time-of-flight (HPLC-TOF), Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR), or gas chromatography – mass spectrometry – infrared spectroscopy (GC-(MS)-IR) condensed phase (US DEA, 2017b; Slovenian National Forensic Laboratory, 2017). The implementation of chromatographic techniques, infrared and nuclear magnetic resonance spectrometry allow unambiguous differentiation between 2- and 3-tetrahydrofuranylfentanyl. A deuterated form, tetrahydrofuran fentanyl-d5, is available for use as an internal standard for the quantification of tetrahydrofuran fentanyl via GC- or LC-MS (EMCDDA-Europol, 2017; USA DEA, 2017a).

3. Ease of Convertibility Into Controlled Substances

At the time of the report, there is no information on whether tetrahydrofuranyl fentanyl is converted into controlled substances.

4. General Pharmacology

A. Routes of administration and dosage

Tetrahydrofuranyl fentanyl has been seized as a liquid, in powder form, and as disk-shaped tablets (pink color, ~5.5mm diameter). Based on forensic reports and paraphernalia found at overdose sites, routes of administration appear to be intravenous, oral, and as a nasal spray. The nasal spray confiscated contained 130 mg/10 ml (EMCDDA-Europol, 2017; USA DEA, 2016, USA DEA, 2017a). In the STRIDA project study, with analytically confirmed existence of tetrahydrofuranyl fentanyl, the authors observed higher serum concentrations of tetrahydrofuranyl fentanyl compared with acrylfentanyl in the intoxication cases suggesting tetrahydrofuranyl fentanyl may be a less potent opioid receptor agonist (Helander et al., 2017). Similarly, self-reports posted on Swedish Internet drug discussion forums in August 2016 and the claimed contents of tetrahydrofuranyl fentanyl on the NPS vendor websites (60–100 mg/10 mL for nasal sprays, and 4–10 mg for tablets) suggests that tetrahydrofuranyl fentanyl might be less potent than acrylfentanyl. However, these estimates should be viewed with caution as verified potency comparisons are not currently available.

B. Pharmacokinetics

Tetrahydrofuranyl fentanyl is expected to be lipophilic; however, no pharmacokinetic studies have been performed at the time of this report. The only data related to pharmacokinetics comes from one 26 year old male patient in Sweden who had overdosed with tetrahydrofuranyl fentanyl using a nasal spray in October 2016. The patient had 45 ng/mL of tetrahydrofuranyl fentanyl in serum and 136 ug/mmol creatinine of tetrahydrofuranyl fentanyl in the urine after a self-report of 8 sprays of liquid. However, the actual concentration in the nasal spray were unknown (Helander et al., 2017).

C. Pharmacodynamics

In radioligand binding assays, Ki values for tetrahydrofuranyl fentanyl were: 0.95 ± 0.32 nM for MOR using [3H]DAMGO; 741 ± 44 nM for KOR using [3H]U69,593; and, 1,730 ± 260 nM for DOR using [3H]DPDPE. Therefore, tetrahydrofuranyl fentanyl selectively bound to μ-opioid receptors when [3H]-DAMGO was used as the radioligand.

When tetrahydrofuranyl fentanyl was evaluated in a [35S]GTPγS functional assay using preparations of transfected Chinese hamster ovary cells expressing human δ- and κ-opioid receptors and rat μ-opioid receptors, tetrahydrofuranyl fentanyl produced 16.2 ± 3.7%, 62.1 ± 5.3%, and 73.8 ± 5.0% maximum stimulation with EC50 potencies of 1440 ± 550 nM, 5,790 ± 430 nM, and 89 ± 16 nM, respectively

(DEA-VA, 2017a, b, c). In summary, tetrahydrofuranyl fentanyl was most effective and most potent at μ-opioid receptors (USA DEA, 2017d).

5. Toxicology

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

6. Adverse Reactions in Humans

Similar to other opioids, the most serious acute health risk from using tetrahydrofuranyl fentanyl is respiratory depression, which in overdose could lead to apnea, respiratory arrest, and death ((EMCDDA-Europol, 2017; Pattinson, 2008; White and Irvine, 1999). For tetrahydrofuranyl fentanyl, the risk may be increased due to some difficulty in diluting the substance, 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 the most adverse effects and overdose cases for tetrahydrofuranyl fentanyl. In total, 14 deaths with confirmed exposure to tetrahydrofuranyl fentanyl were reported occurring between 2016 and 2017. In at least 12 cases, tetrahydrofuranyl fentanyl was the cause of death or contributed to the death. Most of the individuals were found deceased in their homes; 8 were male (57%) aged between 25 and 41 years (mean 31.4, median 29) and 6 were female (43%) aged between 29 and 38 years (mean 31.5, median 30). Other substances were detected in the deaths, including other central nervous system depressants, while other opioids were only detected in 3 cases (EMCDDA-Europol, 2017; USA DEA, 2017a).

The Swedish STRIDA project monitors the occurrence and health hazards of novel psychoactive substances in their country, through evaluation of analytically confirmed serious adverse events presenting in the emergency department and intensive care units. Consistent with previous cases involving fentanyl analogues and derivatives (Bäckberg et et al., 2015, Helander et al. 2016), typical opioid overdose symptoms of CNS and respiratory depression and miotic pupils were observed but tachycardia and hypertension were also common. In this report, tetrahydrofuranyl fentanyl was analytically confirmed in biological samples obtained from an intoxication case where respiratory depression and decreased consciousness were noted. One 26 year old male patient in the STRIDA study had overdosed with tetrahydrofuranyl fentanyl using a nasal spray in October 2016. The patient had 45 ng/mL of tetrahydrofuranyl fentanyl in serum and 136 ug/mmol creatinine of tetrahydrofuranyl fentanyl in the urine after a self-report of 8 sprays which resulted in naloxone reversible (0.2 mg) reduced consciousness at the hospital, miotic pupils, respiratory depression and BPM 110 (Helander, 2017).

Reports collected by the United States DEA indicate that tetrahydrofuranyl fentanyl is being abused for its opioid properties and has resulted in mortality. The DEA collected post-mortem toxicology and medical examiner reports on two confirmed fatalities associated with tetrahydrofuranyl fentanyl which occurred in New Jersey and Wisconsin. However, the DEA states that it is likely that the prevalence of the tetrahydrofuranyl fentanyl in opioid-related emergency room admissions and deaths is underreported as standard immunoassays may not differentiate tetrahydrofuranyl fentanyl from fentanyl (US-DEA, 2017a,b).

In addition to the adverse effects related to respiratory depression, material safety sheets from Cayman Chemical (Ann Arbor, MI USA) report that tetrahydrofuranyl fentanyl may be irritating to the mucous membranes and upper respiratory tract and caution should be taken when handling. Tetrahydrofuranyl 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 exists from adverse effects reports in humans, dependence potential for tetrahydrofuranyl fentanyl is likely high as tetrahydrofuranyl 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

The USA DEA is currently working on testing tetrahydrofuranyl fentanyl in rats trained to discriminate morphine; however, the results of these studies are not available at the time of the report (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

Tetrahydrofuranyl fentanyl 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)

To date, Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Spain, Sweden and the United Kingdom reported that tetrahydrofuranyl 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, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom reported that tetrahydrofuranyl 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 tetrahydrofuranyl 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 neither human nor veterinary use through the centralized procedure. The EMA reports that to date, tetrahydrofuranyl fentanyl only reported use is as an analytical reference material for scientific research (EMCDDA-Europol, 2017).

There are currently no investigational new drug applications or approved new drug applications for tetrahydrofuranyl fentanyl based on a review by the United States Food and Drug Administration. Taken together from the available information, tetrahydrofuranyl fentanyl does not appear to be used in the manufacture of a medicinal product in the European Union or the United States. 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 tetrahydrofuranyl fentanyl besides as an analytical reference standard for scientific research and forensic applications. Tetrahydrofuranyl fentanyl-d5 is also available for use as an internal standard for the quantification of tetrahydrofuranyl fentanyl using GC- or LC-MS methods for research and forensic purposes. Tetrahydrofuranyl fentanyl currently is available for purchase synthesized by various chemical companies available in wholesale amounts and in consumer amounts.

13. Non-Medical Use, Abuse and Dependence

In different countries of countries in East Asia, Europe, and North America between 2012 and 2016, multiple fentanyl analogues were reported to the UNODC early warning advisory on new psychoactive substances. These synthetic opioids, such as tetrahydrofuranyl fentanyl, are most commonly sold as adulterated/substituted heroin or counterfeit prescription pills in North America whereas in Estonia, illicitly produced fentanyl analogues are sold as the drug of choice (UNODC, World Drug Report 2017). Tetrahydrofuranyl 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 a 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 (e.g., http://drugs.tripsit.me/tetrahydrofuran-fentanyl). The population likely to abuse tetrahydrofuranyl 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 tetrahydrofuranyl fentanyl overdose cases.

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

In individuals who may initiate or use a drug for the first time, tetrahydrofuranyl fentanyl use is likely to be at risk for overdose, and death similar to that of other opioid analgesics (e.g., fentanyl, morphine, etc.). As tetrahydrofuranyl fentanyl is available in liquid form as ready-to-use nasal sprays and e-liquids for vaping, this formulation may make them more acceptable to use (Zawilska, 2017). Similar to other fentanyls, accidental exposure to tetrahydrofuranyl fentanyl may also pose a risk of severe poisoning. Those at risk may include law enforcement, emergency personnel, medical and forensic laboratory personnel, postal workers and the friends and family of users (EMCDDA-Europol, 2017; 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.

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

15. Licit Production, Consumption and International Trade

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

16. Illicit Manufacture and Traffic and Related Information

Tetrahydrofuranyl 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 (UNODC, World Drug Report 2017). Europol received reports from Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, Germany, Greece, Latvia, Lithuania, Luxembourg, Romania, Slovakia, and Spain that they have no available information on tetrahydrofuranyl fentanyl. Slovenia provided information on a collected sample, however, they reported no information on production, distribution, or trafficking (EMCDDA-Europol, 2017). However, there have been reports of seizures and illicit traffic as listed below.

In total, the EMCDDA reported 43 seizures of tetrahydrofuranyl fentanyl by Swedish police force, 26 seizures in 2016 and the remaining 17 in 2017. The seizures of tetrahydrofuranyl fentanyl included 41 seizures of liquids, amounting to a total of 698.5 mL and 2 seizures of powders, amounting to a total of 1.57 g. In all the cases, tetrahydrofuranyl fentanyl was the sole substance detected but no quantitative information on purity was reported. Austria, Slovenia, and Sweden reported that tetrahydrofuranyl fentanyl is currently part of routine screening in some (but not all) laboratories.

The commercial, web-based laboratory information management system STARLiMS used by the United States DEA, registered five reports containing tetrahydrofuranyl fentanyl from Florida and Missouri. The first US laboratory submissions of tetrahydrofuranyl fentanyl occurred in March 2017 according to STARLiMS. In January 2017, The National Forensic Laboratory Information System (NFLIS) registered two reports containing tetrahydrofuranyl fentanyl from state or local forensic laboratories in New Jersey. The DEA is not aware of any laboratory identifications tetrahydrofuranyl fentanyl prior to 2017. Together, STARLiMS and NFLIS record seven drug reports in which tetrahydrofuranyl fentanyl was identified in drug exhibits submitted to forensic laboratories in 2017 from law enforcement encounters in Florida, Missouri, and New Jersey.

Slovenia reported a collected sample which consisted of 5 grams of powder and 4-ANPP precursor test-purchased from the internet from a site based in China. In September 2016, Swedish officials test-purchased tetrahydrofuranyl fentanyl as disk-shaped tablets (pink color, ~5.5mm diameter) and a nasal spray (white plastic nasal spray flask without label) from a Swedish NPS website to use as reference materials for the estimation of tetrahydrofuranyl fentanyl and comparison with an absolute area response for a fentanyl standard in LC-HRMS, as previously described (Helander et al., 2016) for the STRIDA analysis of overdose incidences (Helander et al., 2017).

17. Current International Controls and Their Impact

THF-F is not controlled under the 1961, 1971 or 1988 United Nations Conventions. Two possible precursors of fentanyl and potentially tetrahydrofuranyl 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 tetrahydrofuranyl fentanyl into Schedule I on September 12, 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 tetrahydrofuranyl fentanyl (US-DEA, 2017c).

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol added tetrahydrofuranyl 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. Latvia, Sweden and the United Kingdom reported that tetrahydrofuranyl fentanyl is controlled under drug control legislation. Austria and Poland reported that tetrahydrofuranyl fentanyl is controlled under specific new psychoactive substances control legislation and Norway reported that tetrahydrofuranyl fentanyl is controlled under medicines legislation. However, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovenia, Spain, and Turkey reported that tetrahydrofuranyl fentanyl is not subject to control measures at the national level. The EMCDDA and Europol continues to monitor tetrahydrofuranyl 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.

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

Because abusers of tetrahydrofuranyl fentanyl are likely to obtain these substances through unregulated sources and in 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 tetrahydrofuranyl fentanyl, increasing the risk for harmful adverse events.

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

Please refer to separate Annex 1 document published on ECDD website