

U-47700

Critical Review Report

Agenda Item 4.1

Expert Committee on Drug Dependence
Thirty-eighth Meeting
Geneva, 14-18 November 2016

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Summary

U-47700 is 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide. It has two chiral centers with four stereoisomers. U-47700 has no authorizations as a medicinal product/medicine. Reports of its evaluation in controlled, systematic preclinical and clinical abuse-related procedures are not available. However, in other ways it has properties similar to those of an opioid analgesic, and has demonstrated effects that could be interpretable to be similar to the ill effects of compounds in Schedule I of the 1961 United Nations Single Convention such as morphine and AH-7921, the latter of which is a structural isomer.

Some of these preclinical effects include:

1. U-47700 binds to the mu opioid receptor (MOR) with a K_i (\pm SEM) of 0.91 nM (\pm 0.11), much less well to the kappa opioid receptor (KOR) at 110 nM (\pm 11), and poorly so to the delta opioid receptor (DOR) at 480 nM (\pm 110). In comparison, morphine has K_i (\pm SEM) values at the MOR, KOR, and DOR of 0.213 (\pm 0.019), 27.9 (\pm 2.7), and 111 (\pm 14) nM, respectively.
2. It has *in vitro* functional activity at the MOR, KOR, and DORs in the [³⁵S]GTP γ S assay with EC_{50} 's (\pm SEM) of 140 (\pm 23), 201 (\pm 74), and 4,540 (\pm 350) nM, respectively. For morphine as a comparator, these values are 31.0 (\pm 8.2), 83 (\pm 23), and 870 (\pm 140) nM, respectively.
3. U-47700 has antinociceptive activity with ED_{50} 's of 0.2, 0.2 and 0.2 mg/kg s.c. in the tail flick, tail pinch and HCl writhing assays, respectively. It is about 7.5x more potent in the mouse-tail flick assay than morphine.

Some of these clinical effects include:

1. U-47700 has demonstrated opiate-like adverse effects including pinpoint pupils, respiratory depression, cyanosis, and depressed consciousness.
2. The opiate-like adverse effects of U-47700 are rapidly reversed with administration of the opioid antagonist, naloxone.
3. There have been several (>15) confirmed fatalities associated with the presence of U-47700 in Europe and in the United States.

In addition, there is evidence of its sale and distribution.

1. U-47700 is aggressively promoted and sold via the Internet.
2. When promoted and sold, U-47700 has been marketed as a heroin or an oxycodone substitute, as itself, or in combination with other drugs such as fentanyl.
3. There have been several seizures of U-47700 including in Belgium, United States, United Kingdom, and Sweden.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

82657-23-6 (*trans*)

121348-98-9 (*form not specified*)

C. Other Chemical Names

3,4-dichloro-N-[(1R,2R)-2-(dimethylamino)cyclohexyl]-N-methylbenzamide(*trans*)

Benzamide, 3,4-dichloro-N-(2-(dimethylamino)cyclohexyl)-N-methyl-

CHEMBL277572 (*trans*)

SCHEMBL11054573 (*trans*)

3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide

Benzamide, 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methyl-

D. Trade Names

None.

E. Street Names

U-47700

Fake morphine

U4

F. Physical Appearance

White powder is supplied by some online vendors; one vendor supplies U- 47700 as a liquid for use in inhalers in which a user reported that the liquid tasted “minty” perhaps because of adulterants.⁽¹⁾

G. WHO Review History

U-47700 was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that U-47700 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

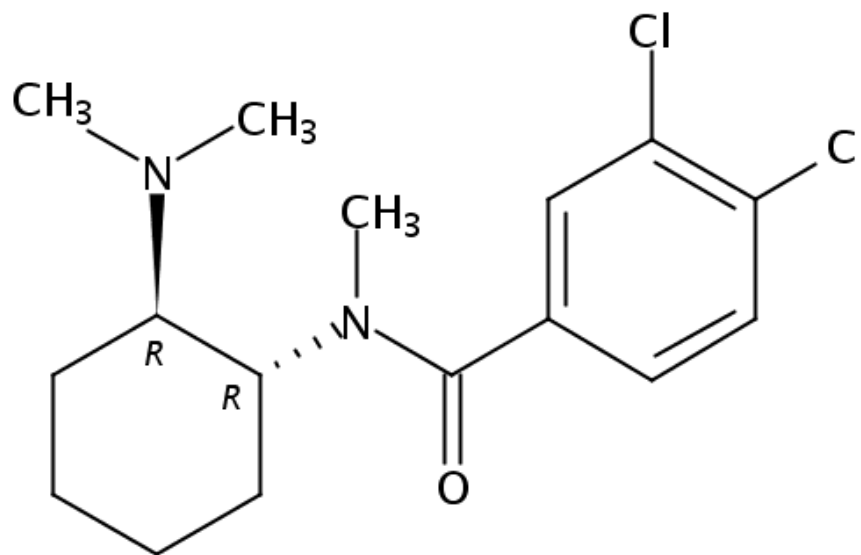
IUPAC Name: 3,4-dichloro-N-[(1R,2R)-2-(dimethylamino)cyclohexyl]-N-methylbenzamide (CAS 82657-23-6 *trans*)

3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide (undefined)

CA Index Name: Benzamide, 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methyl-

B. Chemical Structure

Free base (*trans*):



Molecular Formula: C₁₆ H₂₂ Cl₂ N₂ O

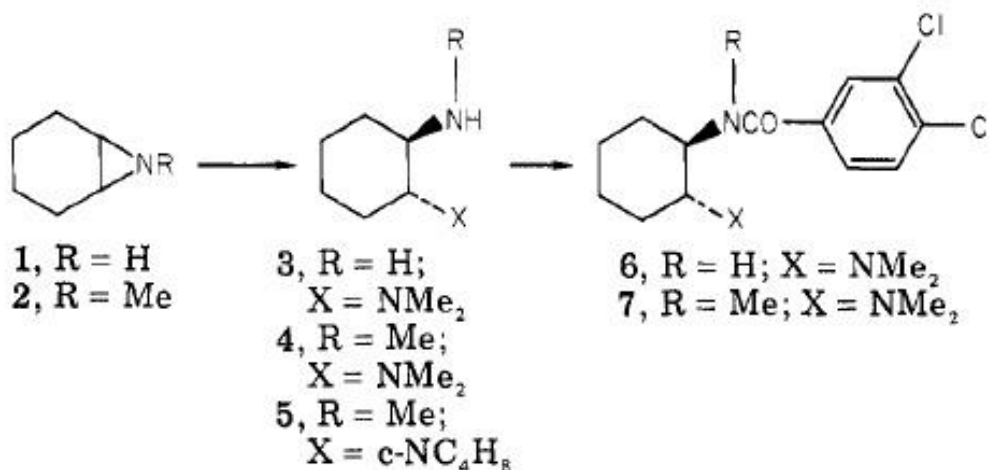
Molecular Weight: 329.26

C. Stereoisomers

Two chiral centers at the bonds to the two nitrogens off the ring resulting in four isomers; *cis* and *trans* each have two enantiomers [*cis*: are (1R,2R), and (1S,2S); *trans* are (1R,2S) and (1S,2R)]. The absolute configuration of the μ agonist enantiomer was originally reported as R,R.⁽²⁾

D. Methods and Ease of Illicit Manufacturing

Szmuszkovicz and VonVoightlander described one of the earliest syntheses as follows, and as refers to the synthetic scheme below: Reaction of the aziridine (compound #1) with dimethylamine gives the *trans* diamine (compound #3). Reaction of compound #3 with ethyl formate gives *trans*-N-[2-(dimethylamino)cyclohexyl] formamide, Reduction with lithium aluminum hydride in ether results in N',N,N'-trimethyl-1,2-cyclohexanediamine (compound #4). Reaction of compound #4 with 3,4-dichlorobenzoyl chloride gives U-47700 (i.e., compound #7; 3,4-dichlorobenzamide).⁽³⁾



Synthesis of U-47700 taken from Szmuszkovicz and Von Voigtlander, 1982.⁽³⁾

E. Chemical Properties

Melting point: 97-98.5°C (trans)⁽⁴⁾

Flash point: 234.9±28.7 °C⁽⁵⁾

Boiling point (predicted): 464.8±45.0 °C | Condition: Press: 760 Torr (trans, CAS Registry Number 82657-23-6)⁽⁵⁾

Solubility: Sparingly Soluble (0.49 g/L) Unbuffered Water pH 10.36/Temp: 25°C; Very Soluble (527 g/L) pH 4/Temp: 25 °C. (trans, CAS Registry Number 82657-23-6)⁽⁵⁾

Density (Predicted) Value: 1.22±0.1 g/cm³ Condition: Temp: 20 °C Press: 760 Torr⁽⁵⁾

F. Identification and Analysis

Extraction and detection techniques with U-47700 have been reported in a number of studies.⁽⁶⁻¹⁰⁾ A recent report by Mohr and colleagues (2016)⁽⁷⁾ provides details in which LCMSMS was used where the limit of detection in blood of U-47700 was 0.5 ng/mL. The calibration performance over 3 days of replicates resulted in average correlation coefficient of 0.9995. AH-7921, a structural and abused isomer of U-47700, did not meet acceptance criteria for retention time. This was verified with U-47700 standard reference material. This method was used to confirm the presence of U-47700 in 11 postmortem cases.⁽⁷⁾

Currently deployed, routine detection methods may be unable to detect the presence of U-47700 and may actually give false negatives for it, and false positives for others. For example, Schneir and colleagues used a urine drugs of abuse panel by immunoassay (Roche ONLINE DAT Plus performed on a Cobas 6000 analyzer, Roche Diagnostics International Ltd. Switzerland) on a 22 year-old man who had likely overdosed with U-47700 (see Section #6).⁽⁶⁾ The man's urine was positive for benzodiazepines as a class, but negative for amphetamines as a class, barbiturates as a class, benzoylecgonine (cocaine metabolite), methadone, opiates as a class, oxycodone, phencyclidine, and tetrahydrocannabinoids. Subsequent analysis indicated the indication of benzodiazepine presence was a false positive and the authors speculated that a metabolite of U-47700 might have been responsible for

the cross-reactivity. Further analysis of urine was performed using a broad-spectrum liquid chromatography time-of-flight (LC-TOF) high-resolution mass spectrometry assay that indicated urine was negative for sixty-one compounds that have been validated for this assay but confirmed the presence of a compound with the molecular formula C₁₆H₂₂C₁₂N₂O, which matches that of U-47700.⁽⁶⁾

Reference standards are available.

3. Ease of Convertibility Into Controlled Substances

The closest controlled substance structurally to U-47700 is AH-7921, and they are structural isomers of one another. AH-7921 was placed into Schedule I of the 1961 Single Convention, as amended by the 1972 Protocol, in 2015. It would be extremely difficult to convert U-47700 into AH-7921 based upon expert opinion.⁽¹¹⁾

4. General Pharmacology

A. Routes of administration and dosage

From user reports: Oral, insufflation, intravenous, rectal (e.g.,¹²), and via an inhaler using a liquid solution⁽¹⁾ have been used.

In terms of route of administration (ROA) and potency relationships, a user reported: “Also in my experience with the ROAs I tried, I found the strength something like this: IV : Snorted : Plugged : Oral 1 : 2 : 2.5 : 3-4+”⁽¹²⁾

In terms of user reports of potency and dosage, one commented: “...quite potent (definitely not 7.5x morphine, closer to 2.5x, dose is 10-25mg)”⁽¹³⁾ For potency estimates using *in vivo* laboratory animal procedures, see Section 4C below.

B. Pharmacokinetics

Controlled, systematic pharmacokinetic studies have not been reported using neither laboratory animals nor human subjects. Information regarding the metabolism of U-47700 can be obtained from case studies involving U-47700 usage. Jones and colleagues have reported detected metabolites of U-47700 in urine and serum of a 23 year-old female who had insufflated and intravenously administered U-47700.⁽⁸⁾ The excretion of U-47700 was found to be dominated by a demethylated metabolite, identified as "M1" shown in Table 2 from the Jones and colleague's study reproduced below. The demethylated compound was further metabolized to four isomers of a hydroxylated metabolite, M3–M6. Two primary and two minor isomers were detected. For each isomer, the site of hydroxylation was deduced to be on the cyclohexyl ring of U-47700; however, the exact sites of metabolism could not be further refined via mass spectrometry. Also detected was a bisdesmethyl metabolite, M2, and four corresponding hydroxylated metabolites, M7–M10. No phase II glucuronide metabolites were detected in the urine sample. As seen in Table 2 from the Jones and colleague study, U-47700 was detected at 394 ng/mL and 228 ng/mL in serum and urine, respectively. Metabolites detected in appreciable amounts included the desmethyl (1964 ng/mL in urine), bisdesmethyl (618 ng/mL), desmethyl hydroxy (447 ng/mL), and bisdesmethyl hydroxy forms (247 ng/mL) of U-47700.⁽⁸⁾

Table 2. Measured drug levels and estimated metabolite levels.

	Urine concentration (ng/mL)	Serum concentration (ng/mL)
U-47700	394	228
M1; Desmethyl U-47700	1964 ^a	27 ^a
M2; <i>N,N</i> -Bisdesmethyl U-47700	618 ^a	N/D
M3–M6; Desmethylhydroxy U-47700	447 ^{a,b}	N/D
M7–M10; <i>N,N</i> -Bisdesmethyl hydroxy U-47700	247 ^{a,b}	N/D

^aApproximate concentration based on the response of U-47700.

^bConcentration estimate of the sum of four detected hydroxylated isomers.

Table 2 from Jones et al., 2016.⁽⁸⁾

Given the lack of controlled laboratory animal or human pharmacokinetic studies, time course effects of U-47700 remain speculative and based upon reported user experiences. A sampling of user reports on drug forums typically have reported a short duration of action for U-47700, and shorter than that of heroin.^(e.g., 1, 13)

C. Pharmacodynamics

Loew and colleagues evaluated U-47700 for its *in vitro* binding activity using guinea pig brain at the mu opioid receptor (MOR) and the kappa opioid receptor (KOR). U-47700 had high affinity at the MOR and bound with a K_D of 5.3 nM and weakly at the KOR with a K_D of 910 nM resulting in a >171x preference for the MOR relative to the KOR.⁽¹⁴⁾ Subsequently these researchers reported U-47700 receptor affinities (IC₅₀s) of 9 and 300 nM, respectively, for the MOR and KORs.⁽¹⁵⁾

In a recent (March 2016) unpublished study, Janowsky provided *in vitro* binding and *in vitro* functional activity results for U-47700 at mu, kappa, and delta opioid receptors.⁽¹⁶⁾ Receptor binding studies were conducted using human delta opioid receptors (DOR) and KORs transfected into Chinese hamster ovary (CHO) cells, and rat MORs transfected into CHO cells. Binding assays were conducted using [³H]DPDPE (0.8 nM, ~20,000 cpm), [³H]U69,593 (0.8 nM, ~22,000 cpm) and [³H]DAMGO (0.8 nM, ~20,000 cpm) for the DOR, KOR, and MORs, respectively. Stimulation of [³⁵S]GTPγS was also evaluated using the respective CHO cells for determining functional activity at each of the opioid receptors. U-47700 potently bound to the MOR with a K_i (±SEM) of 0.91(±0.11) nM, much less well to the KOR at 110 nM(±11), and poorly so to the DOR at 480 nM (±110). In comparison, morphine had K_i (±SEM) values at the MOR, KOR, and DORs of 0.213 (±0.019), 27.9 (±2.7), and 111 (±14) nM, respectively. Functional activity results at the MOR, KOR, and DORs in the [³⁵S]GTPγS assay [EC₅₀ (±SEM)] for U-47700 were 140 (±23), 201 (±74), and 4,540 (±350) nM, respectively, and for morphine as a comparator, 31.0 (±8.2), 83 (±23), and 870 (±140) nM, respectively.⁽¹⁶⁾

Cheney and colleagues examined the binding characteristics of U-47700 competing with [³H]naloxone in rat brain homogenates, and evaluated its analgesic effects in male CF-1 mice using the tail-flick test using focused high-intensity light as the aversive stimulus.⁽⁴⁾ Analysis of the binding results was carried out in terms of a two-state receptor model by means of an iterative nonlinear regression technique fitting the theoretical model to the experimental binding data.⁽⁴⁾ The parameters determined in this procedure were the affinity constants for the agonist and antagonist states of the receptor. A 27x greater affinity was

calculated for the “agonist-state” vs the “antagonist-state”⁽⁴⁾ and was less potent than morphine for both states. U-47700 demonstrated potent antinociception in the mouse tail-flick test with an ED₅₀ of 0.2 mg/kg s.c. that was 7.5 more potent than morphine, and produced characteristic MOR agonist effects of Straub tail, arched back and elevated locomotor activity.⁽⁴⁾ U-47700 was ineffective (ED₅₀ > 100 mg/kg) in antagonizing morphine’s antinociceptive effects.

Szmuszkovicz and VonVoightlander also reported potent analgesic activity in the mouse with U-47700 with ED₅₀ ‘s of 0.2, 0.2 and 0.2 mg/kg s.c. in the tail flick, tail pinch and HCl writhing assays, respectively. U-47700 also caused mice to fail the inclined screen test with an ED₅₀ of 9.0. The inclined screen test is used as a test for sedative-like activity. In addition, U-47700 showed full morphine-like effects on overall appearance by inducing Straub tail, arched back and increasing locomotion.⁽³⁾

5. Toxicology

Controlled, systematic preclinical or clinical toxicological studies could not be found using U-47700. Currently available (August, 2016) sample safety sheets from a legitimate provider of U-47700 indicated, “To the best of our knowledge, the toxicological properties have not been thoroughly investigated.”⁽¹⁷⁾

6. Adverse Reactions in Humans

One of the earliest case reports of a patient presenting with an opioid-like toxidrome associated with U-47700 use was by Armenian and colleagues.⁽¹⁸⁾ In their case, a 41-year old woman presented to an emergency department in Northern California after consuming three pills she thought were “Norco” pills, a street name referring to pills containing fentanyl and various amounts of acetaminophen and hydrocodone. She had regularly been purchasing acetaminophen-hydrocodone combination pills on the street for chronic back pain and took 2-3 at a time, 2-3 times a day. She presented with pinpoint eyes, respiratory depression, and depressed consciousness. She promptly awoke and was able to answer questions following intravenous administration of 0.4 mg of naloxone. During the subsequent two hours, she remained somnolent but was able to wake up and speak coherently. Serum samples were analyzed with liquid chromatography–quadrupole time-of-flight mass spectrometry (LC 1260 QTOF/MS 6550; Agilent, Santa Clara, CA) that screened for 581 drugs including 303 “designer” drugs. Suspect screening for 54 opioid analogues was also conducted. Results were significant for the presence of fentanyl (15 ng/mL) and U-47700 (7.6 ng/mL), along with several other drugs including acetaminophen, benzoylcegonine, gabapentin, hydrocodone, and sertraline.⁽¹⁸⁾

Another report of toxic use presumably of U-47700 was of a 22-year old man with a history of heroin abuse who was found unconscious and apneic by his mother.⁽⁶⁾ Paramedics administered 2 mg of naloxone intravenously that completely reversed his coma and bradypnea. The patient reported that just before being found by his mother, he had used U-47700 he had acquired over the Internet. He described having purchased what he interpreted as 250 mg of the drug in powder form, which he divided into five separate doses. He had administered the drug by placing it in a syringe, mixing with water, and applying to his nostrils. A urine drugs of abuse panel by immunoassay (Roche ONLINE DAT Plus performed on a Cobas 6000 analyzer, Roche Diagnostics International Ltd.

Switzerland) was positive for benzodiazepines as a class, but negative for amphetamines as a class, barbiturates as a class, benzoylecgonine (cocaine metabolite), methadone, opiates as a class, oxycodone, phencyclidine, and tetrahydrocannabinoids. Subsequent analysis indicated the indication of benzodiazepine presence was a false positive and the authors speculated that a metabolite of U-47700 might have been responsible for the cross-reactivity. Further analysis of urine was performed using a broad spectrum liquid chromatography time-of-flight (LC-TOF) high-resolution mass spectrometry assay that indicated urine was negative for sixty-one compounds that have been validated for this assay but confirmed the presence of a compound with the molecular formula $C_{16}H_{22}N_2O$, which matches that of U-47700. A reference standard for U-47700 could not be obtained at the time, but one was used for the abused new psychoactive substance NPS, AH-7921, that has the same molecular formula but different structure. Analysis ruled out the presence of AH-7921. Ultimately, the patient had been resuscitated quickly with the aid of naloxone, and appeared to not suffer permanent sequelae.⁽⁶⁾

Other recent studies have reported adverse effects of U-47700 following acute administration. A 26-year old man and a 24 year-old woman had consumed alcohol and alprazolam and then insufflated a powdered substance they thought to be “synthetic cocaine” that was named U-47700 when purchased online.⁽¹⁹⁾ After insufflation of the U-47700, the woman described feeling “cool and relaxed”, which surprised her as this was comparable to heroin and she was expecting a stimulant. She had used heroin in the distant past. She fell asleep after use of U-47700, and awoke approximately 3 h later. She was subsequently transported to the emergency department where she reported anxiety, nausea, shivering and abdominal pain. Immediate effects of U-47700 were not reported in the male patient. Approximately 3 h after he had insufflated U-47700, the man was found face down on the lawn with agonal breathing and cyanosis. Emergency Medical Services (EMS) was called, and the providers reported the man to be cyanotic with oxygen saturation of 50% on ambient air. A 28 panel immunoassay test used on the man's urine was positive for benzodiazepines, cannabinoids and ketamine. LC/MS/MS testing detected lorazepam, cotinine, ketamine, norketamine and U-47700. U-47700 was detected in the male patient's urine at 0.1 ng/mL. GC-MS detected the presence of propofol and acetaminophen. LC/QToF qualitative analysis detected the presence of acetaminophen, ketamine, ketorolac, ofloxacin, piperacillin and U-47700. Consistent with the analytical findings, this patient had received lorazepam and ketamine during intubation in the emergency department and was sedated with propofol during admission. GC-MS analysis was not performed on the woman's urine due to insufficient sample volume. Immunoassay tests of the woman's urine were positive for cannabinoids. LC/MS/MS analysis detected only cotinine. LC/ QToF analysis of the woman's urine detected acetaminophen, ketorolac, piperacillin, theobromine and U-47700. Both urine samples were negative for other opioids.⁽¹⁹⁾

Elliott and colleagues reported one of the earliest fatalities associated with U-47700.⁽⁹⁾ A 27-year old male was found dead in his home in January 2016. Routine toxicological analysis of the post-mortem urine or blood detected quetiapine, amphetamine, amitriptyline, naproxen, mexedrone and ketamine. Ethanol was not detected. Analysis confirmed the primary compound detected in powder taken from the decedent's nasal passage and his post-mortem blood and urine to be U-47700. Quantitative analysis by HPLC-DAD of post-mortem femoral blood measured U-47700 at a concentration of 1.46 mg/L. These researchers concluded, “The major risk to life from opioids is their depressant

effect on the central nervous system, notably causing respiratory depression, and in the absence of any other significant pathological or toxicological findings, fatal U-47700 toxicity was a likely outcome."⁽⁹⁾

Approximately at the same time as Elliott and colleagues reported a U-47700-associated death⁽⁹⁾, Coopman and colleagues had reported another.⁽¹⁰⁾ In this instance, a 30-year old man was found dead on the ground of a storage room in his house. Drug paraphernalia were present on the table in the decedent's living room including a recently delivered envelope from China, a white powder (36 g), a digital scale and spoon. No injection sites or traumatic injuries were evident. A charred piece of aluminum foil was found nearby suggesting the use of a substance by vaporization. Blood and urine were taken by the medical examiner during the external body examination and submitted for a comprehensive systematic toxicological analysis. Police investigation revealed that the man searched the internet for information on new psychotropic substances, among others including U-47700. A powder found in the victims' home was transferred to the laboratory for analysis, in which trace amounts of fentanyl (0.0035%, m/m) and U-47700 (0.0012%, m/m) were identified by gas chromatography mass spectrometry. A toxic fentanyl level of 10.9 µg/L and a therapeutic level of 180 µg/L of sertraline were measured in the subclavian blood. The target analysis performed by UPLC-MS/MS revealed the presence of U-47700 at a concentration of 13.8 µg/L in blood and 71.0 µg/L in urine. The authors reported, "Based on circumstantial evidence (police investigation, crime scene) and the results of the toxicological analysis, the medical examiner concluded that the cause of death was an acute intoxication and overdose with fentanyl and U-47700 immediately after inhaling the fumes of the vaporized powder."⁽¹⁰⁾

Ruan and colleagues⁽²⁰⁾ had several criticisms of Coopman and colleagues'⁽¹⁰⁾ conclusions, perhaps the most important was that the blood concentration of U-47700 reported in Coopman's study (13.8 µg/L) was so much lower than that reported in the Elliott and colleagues' study⁽⁹⁾ (1460 µg/L) that it was questionable whether U-47700 really contributed to the death in the decedent. Further, Ruan and colleagues believed, "...that the finding of the blood and urine U-47700 concentrations of 13.8 and 71.0 µg/L, respectively, i.e., 5 times more U-47700 in the urine than in the blood, actually goes against the conclusion of 'acute intoxication and overdose of U-47700'. We believe it is highly unlikely that the death happened 'immediately after inhaling the fumes of the vaporized powder,' in light of the 5 times more U-47700 present in urine than in the blood."⁽²⁰⁾ Ruan and colleagues also wondered if the, "...measured urine U-47700 (5- times higher than in blood) be actually a mixture of U-47700 and U-47700 metabolites?" These observations by Ruan and colleagues⁽²⁰⁾ makes it uncertain to what degree U-47700 actually contributed to the decedent's death in the Coopman report.⁽¹⁰⁾

There have been a few other reports of fatalities in which U-47700 have been associated. The Belgium Early Warning System on Drugs (BEWSD) of the Scientific Institute of Public Health reported in February 2016 that they received information on a fatality involving U-47700 and fentanyl.⁽²¹⁾ Postmortem blood samples, as well as powder seized, revealed the presence of fentanyl and U-47700. The BEWSD advised that the substances were not sold as heroin.⁽²¹⁾ In separate incidents, one 20 and one 27 year-old man were found dead in their homes. Post-mortem analysis of blood identified the presence of U-47700 in each. Analysis of powder found in the vicinity of the 27 year-old decedent indicated the presence of U-47700 and etizolam, although etizolam was not detected in his

blood.⁽²²⁾ In 20 recent postmortem cases in which the decedents were initially believed to be heroin or other opioid-related drug overdoses, U-47700 was the confirmed drug in 11 of the 20 cases, 5 cases of which were confirmed for both U-47700 and furanyl fentanyl⁽⁷⁾. The mean and median blood concentrations for U-47700 were 253 ng/mL (\pm 150) and 247 ng/mL, respectively.⁽⁷⁾ The Drug Enforcement Agency of the United States reported in September of 2016 there had been at least 15 confirmed fatalities in the U.S. associated with U-47700 usage (it is uncertain if the DEA is including the deaths reported in the Mohr and colleagues study⁽⁷⁾ cited above).⁽²³⁾ In their declaration of intent to temporarily place U-47700 in Schedule I of the Controlled Substances Act they declared, "...based on the available data and information...the continued uncontrolled manufacture, distribution, reverse distribution, importation, exportation, conduct of research and chemical analysis, possession, and abuse of U-47700 poses an imminent hazard to the public safety."⁽²³⁾

7. Dependence Potential

A. *Animal Studies*

Controlled, laboratory animal studies regarding the potential physical dependence effects of U-47700 have not been reported. No relevant studies could be identified after minimally searching on "(U-47700) AND (rat OR mouse OR monkey) AND (discrimination OR self administration OR withdrawal OR dependence OR reinforce*)" in Web of Science, PubMed or Scopus databases as the "topic" or in "title+abstract" or in "title+abstract+keywords", respectively, as late as 4 September 2016.

B. *Human Studies*

Controlled, human studies regarding the potential physical dependence effects of U-47700 have not been reported. No relevant controlled human subject studies could be found after minimally searching on "(U-47700 AND (discrimination OR self administration OR withdrawal OR dependence OR reinforce*))" in Web of Science, PubMed or Scopus databases as the "topic" or in "title+abstract" or in "title+abstract+keywords", respectively, as late as 4 September 2016.

Despite the lack of controlled, dependence studies with human subjects, perhaps some insight may be obtained from user reports regarding the induction of tolerance and dependence with U-47700. User reports suggest that U-47700 may induce tolerance and dependence. For example, one user reported, "U-47700 presents a similar problem. Sustained use skyrockets tolerance rendering a previously standard dose of oxycodone for instance, more or less completely useless. Even after rapid taper and abstinence for a few weeks, tolerance appears to remain much higher than before. The strange thing is this seems to take place without the need to increase the dose of U-47700 by much, it definitely is increased but not by a huge amount."⁽²⁴⁾ And as an example of dependence, one user reported the following: "Got a g of u 47700 bout a week and a half ago, and talk about fiendish! I'm usually extremely good at avoiding physical addiction to such substances but I managed to with this one! Currently detoxing myself over the break, runny nose eyes anxiety night sweats insomnia n sore throat (maybe getting sick from compromised immune system?) been using Kratom n ac&c to keep it manageable. Took about 2 days for withdrawal to start for me, but only used 231mgs so far."⁽²⁵⁾

8. Abuse Potential

A. *Animal Studies*

Controlled, laboratory animal studies regarding the abuse potential effects of U-47700 have not been reported. No relevant studies could be identified after minimally searching on “(U-47700) AND (rat OR mouse OR monkey) AND (discrimination OR self administration OR withdrawal OR dependence OR reinforce*) in Web of Science, PubMed or Scopus databases as the “topic” or in “title+abstract” or in “title+abstract+keywords”, respectively, as late as 4 September 2016.

B. *Human Studies*

Controlled, human studies regarding the abuse potential effects of U-47700 have not been reported. No relevant controlled human subject studies could be found after minimally searching on “(U-47700 AND (discrimination OR self administration OR withdrawal OR dependence OR reinforce*)) in Web of Science, PubMed or Scopus databases as the “topic” or in “title+abstract” or in “title+abstract+keywords”, respectively, as late as 4 September 2016 .

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

Although investigated as a potential analgesic in animal models (no clinical investigations), U-47700 has no history as a therapeutic agent. Searching on the terms “U-47700”, the CAS Registry number “121348-98-9”, or the IUPAC Name “3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide” in the European Medicines Agency database, the U.S. FDA database (Drugs@FDA), The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) database of the Australian Government Department of Health, nor the Pharmaceuticals and Medical Devices Agency of Japan yielded any pertinent results suggesting a lack of any current marketing authorizations as a medicinal product or therapeutic applications of U-47700.

10. Listing on the WHO Model List of Essential Medicines

U-47700 is neither listed on the 19th List for Adults, nor on the 5th List for children in the WHO Model List of Essential Medicines.^(26, 27)

11. Marketing Authorizations (as a Medicinal Product)

There are no marketing authorizations as a medicinal product for U-47700 (see also Section #9).

12. Industrial Use

U-47700 has no legitimate industrial use.

13. Non-Medical Use, Abuse and Dependence

U-47700 use and/or seized material have been reported in Belgium, United States, United Kingdom, and Sweden.^(for example see, 8, 9, 10, 28) Perhaps an indicative of non-medical use can be obtained from one seizure of U-47700 during March 2016 in which law enforcement officers in Lorain County, Ohio, U.S.A., seized 500 pills that visually appeared to be oxycodone. The pills were blue and had "A 215" markings, consistent with 30 milligram oxycodone pills. Laboratory analysis indicated that the pills did not contain oxycodone, but were instead U-47700.⁽²⁹⁾

Also refer to 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

There are no reports of systematically collected data regarding the prevalence of U-47700. The broad availability of the drug through the Internet (see Section 16), the mode of use either being marketed as a heroin or an oxycodone substitute, as itself, or in combination with other drugs (see Sections 6, 13 and 16), the many reports of seizures in Europe and North America (see Section 13), the reports of opiate-like adverse effects and associated fatalities (see Section 6), suggests that U-47700 is a public health menace.

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

15. Licit Production, Consumption and International Trade

Other than minimal production as a reference standard, there appears to be no legitimate production, consumption or international trade of U-47700.

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

16. Illicit Manufacture and Traffic and Related Information

U-47700 can be readily obtained through the Internet often supplied via vendors advertised as providing research chemicals. Conducting a search using the Google search engine on the term, "U-47700 for sale", resulted in ~802,000 hits. Sampling the first five hits resulted in vendors obviously trying to sell products marketed as U-47700 [1) U-47700 buy U-47700 for sale online - \$39.20 -Best-Feel.com, 2) U-47700 buy U-47700 online for sale - \$86.80 - BestRCS.com, 3) I just got some U-47700 - AMA : RCSources - Reddit, 4) Buy U-47700 online from Mr Chemistry. - Mrchemistry.com, 5) Buy Online U-47700 USA, UK, EU, AU @ \$8 per g : ChingLabs] (Accessed September 1, 2016). Other researchers have reported the ease of buying U-47700 online for as little as US\$40.⁽¹⁹⁾

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

17. Current International Controls and Their Impact

U-47700 is not controlled under the 1961, 1971 or 1988 United Nation Conventions.

18. Current and Past National Controls

U.S.: U-47700 is currently under petition by the DEA to have it placed into temporary control in Schedule I of the CSA.

U.K.: U-47700 is controlled under the Psychoactive Substances Act 2016

Sweden: U-47700 is controlled under the narcotics law (1968: 64). Regulation (2006: 273).

Also refer to Annex 1: "Report on WHO Questionnaire for Review of Psychoactive Substances for the 38th ECDD: Evaluation of U-47700", for updated listing.

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 38th ECDD: Evaluation of U-47700

Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR) answered the questionnaire regarding U-47700. Of these, 15 respondents (11 EUR, 1 PAH and 2 WPR) had information on the substance.

LEGITIMATE USE

There were 13 countries that reported no approved medical products containing U-47700 for human or veterinarian indications.

U-47700 is not currently being used in any medical or scientific research (excluding use as an analytical reference standard) in 11 countries, or for any industrial purpose in 10 countries.

U-47700 was not reported to be used for any cultural, religious or ceremonial purposes in 14 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 11 countries that reported U-47700 as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are oral (6 countries), injection (5 countries), inhalation (2 countries), sniffing (4 countries), rectal (1 country) and smoking (1 country). The main route of administration for U-47700 was reported as oral (4 countries) followed by injection/intravenously (2 countries) and sniffing (2 countries).

The most common formulation reported for non-medical/non-scientific purposes was powder (7 countries), followed by tablets (2 countries), liquid or solution for oral administration/use (1 country) and injectable solutions (1 country). One country specified the use of U-47700 by nasal spray.

There were 8 countries which reported that the source of U-47700 for non-medical/non-scientific use was smuggling.

One country specified users of prescription opioid analgesics and heroin as a subpopulation known to misuse U-47700.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either substantial (1 country) or serious (7 countries). Countries specified that the substantial or serious level was due to the association of U-47700 with fatalities, adverse events (including respiratory depression) and it is considered a potent opioid. It was mentioned by one country that U-47700 has been marketed in Europe as tablets which resemble less harmful pharmaceutical products thereby making accidental administration more likely.

One country reported a single hospital care visit related to the non-medical use of U-47700. No adverse effects for U-47700 were reported or detailed.

In regards to the mortality rate, data was provided by 5 countries. There were a combined total of 7 cases in 2016 reported where it was unknown if other substances were involved. One country reported 54 fatalities between 2015 and 2016 where it was also unknown if other substances were involved. It was noted by one country that there are probably 2 further fatalities in 2016, but the toxicological analyses are outstanding. Another country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 9 countries which reported that U-47700 was under national control. The legislation that the control is based upon included the Controlled Substances Act (6 countries), Criminal Law Act (1 country), Analog Act (1 country) and other specific legislation (1 country stated that it was New Psychoactive Substance Act). In one country the control is a temporary provision since 2015.

One country reported that a challenge to implementing control for U-47700 was that the Analog Act is often challenged in court cases.

The scope of the controls includes production (6 countries), manufacturing (8 countries), exporting (6 countries), importing (9 countries), distribution (8 countries), use (6 countries) and possession (7 countries).

Reported illicit activities involving U-47700 include trafficking (5 countries), smuggling (1 country), internet sales from abroad (5 countries), internet sales from unknown locations (4 countries) and finally sales to people who use this substance (1 country).

There were 4 countries which completed the section on the number of seizures. The combined number of seizures was 1 (2014), 8 (2015) and 95 (2016 to date).

If U-47700 was placed under international control, 14 countries responded that they would have the capacity to enforce the control at the national level. There were 13 countries which responded that they would have the forensic laboratory capacity to analyse the substance.