

EU EARLY WARNING SYSTEM ALERT

Subject: U-47,700 in Europe

1. Read me first

U-47,700 is a potent opioid sold by online retailers as a 'research chemical'. It was first detected in Europe in October 2014 and has been detected in a total of 9 European countries. Since the end of 2015 there has been an increase in the detections of U-47,700 reported. This includes a seizure of just over 1 kg of powder by customs that originated from China as well as the seizure of more than 2,600 counterfeit diazepam tablets. Finally, 3 deaths where U-47,700 caused or contributed to the death have been reported; these occurred in January and February 2016.

The purpose of this alert therefore is to:

- highlight what is known about U-47,700 on the European drug market;
- provide an overview of the chemistry and methods used in the detection of U-47,700, as well as a discussion of its pharmacology, toxicology, and epidemiology;
- request that you report any additional data you may have on U-47,700 in order to improve our understanding of its use and potential risks. Data should be reported to: ews@emcdda.europa.eu

Finally, it is important to note that you should avoid using terms such as 'potent' or 'strong' to describe U-47,700 in risk communications aimed at users, as such terms may cause users to actively seek out such substances.

2. Data use restrictions

As with all alerts transmitted by the EU EWS, please remember that they may contain information that could be regarded as sensitive. Should you provide some of the information in this alert to other groups we would ask that you exercise your best judgement on what information needs to be provided.

If you have any questions in this respect, please contact us first: ews@emcdda.europa.eu

3. Details of the event(s)

As of the 8th of June 2016, the EMCDDA has received reports of 3 deaths associated with the synthetic opioid U-47,700. The deaths occurred in the first two months of 2016 in three member states (Belgium, Sweden and the United Kingdom).

U-47,700 was analytically confirmed in biological samples in all deaths and in two cases powder samples containing U-47,700 were also recovered at the scene. In one of the cases the sample contained U-47,700 and was recovered from the nostrils of the deceased and in another U-47,700 had been mixed with fentanyl and was recovered from a powder found in the deceased's home. In the latter, aluminium foil with residues of burned powder was also found.

The cause of death was available for the 3 cases. In all of them U-47,700 was reported to be the cause of death or contributing to the cause of death. The route of administration was presumed to be ‘smoking’ in one of the cases and ‘snorting’ in another reported case.

These deaths occur in the context of important seizures of U-47,700 in Europe. In January this year more than 1 kg of U-47,700 as a white powder were seized at Madrid-Barajas Airport in Spain, in transit from China. Between January and March 2016, the Scottish police have reported three different seizures totalling 2,629 tablets appearing to be counterfeit diazepam but containing U-47,700 (see Figure 1). The seizure of these tablets raises concerns as they may be sold on the drug market as diazepam tablets, a benzodiazepine that is widely sought after by a range of users.

4. Detections by the EU EWS Network

Detections of U-47,700 have been reported by 9 Member States (including 1 detection as a ‘collected sample’). Small seizures have occurred at street-level and in amounts over 1 kg at international borders. Most seizures have occurred between the last quarter of 2015 and the first quarter of 2016.

Formal notification

U-47,700 was formally notified by the EMCDDA on behalf of Sweden in January 2015. It was identified in a seizure of 5.3 g of white powder made by Swedish customs in Arlanda on 30 October 2014. The substance was analytically confirmed by GC-MS, GC-IRD, LC-MS and NMR by the National Forensics Centre (NFC).

Serious adverse events

Three deaths associated with the consumption of U-47,700 have been reported to the EMCDDA, all of which were analytically confirmed (see section 3 ‘Details of the events’).

Seizures

Seizures of U-47,700 have been reported to the EMCDDA by Belgium, Denmark, Estonia, Finland, France, Sweden (see ‘Formal Notification’ above), Spain and the United Kingdom.

Over 1 kg was seized in powder form; in addition approximately 260 ml of liquid and 2,626 tablets were seized. The largest single seizure of U-47,700 in powder form was made on 18 January 2016 in Spain (Adolfo Suárez-Barajas Airport, Madrid), where 1.054 kg was seized in transit from China to Barcelona.

2,626 tablets containing U-47,700 were detected by police in Scotland in 3 seizures between January and March 2016 (January, 854 tablets; February, 1014; March, 761) [2,3]. The tablets featured three different designs of counterfeit diazepam: one was white, round and bearing an interlocked “MA” logo (made to look like diazepam commercialised by M&A Pharmachem); another was yellow, round and bearing a “5” logo (made to look like diazepam tablets commercialised by Actavis) (see Figure 1) and another was yellow round, bearing a “COX” logo with a half-score and “DC” marked (opposite unmarked).

Other seizures included:

- white powders (ranging from 0.8 to 10 g), some of which in transit between two European destinations (Belgium to Germany, Belgium to Denmark, United Kingdom to Estonia) or between China and a European destination (China to France and China to Spain);
- seizures of liquids amounting to more than 260 ml (including one seizure of a nasal spray containing acetylfentanyl and butyrlfentanyl; and one seizure of a bottle with a liquid containing acetylfentanyl and U-47,700).

Collected samples

Slovenia reported a collected sample of 1 g of U-47,700 in powder form which was test-purchased as part of the EU co-funded project RESPONSE, on 9 December 2015. The sample was purchased on the internet, from a website appearing to be based in China.

5. Names of substance and other identifiers

- IUPAC name: 2-(3,4-dichlorophenyl)-N-[(1R,2R)-2-(dimethylamino)cyclohexyl]-N-methylacetamide
- Common name: U-47,700 ; U-47700
- Other names: 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide; trans-3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methyl-benzamide
- CAS Registry number: 82657-23-6 (HCl salt); 121348-98-9 (free base)

6. Substance classification

Opioid

7. Chemistry and analysis

U-47,700 was patented in the 1970's by Upjohn [4] in the context of a series of studies of (2-aminocycloaliphatic) benzamides and naphthamides. Similarly to AH-7921, U-47,700 is a derivative of dimethylaminocyclohexane to which a 3,4-dichlorobezanamide moiety is appended (Note: AH-7921 has been risk assessed by the EMCDDA in 2014 and has subsequently been added to schedule I of the UN Single Convention on Narcotic Drugs of 1961) [5].

U-47,700 has two chiral centres and can occur as geometric ("cis, trans") diastereomers (whereby different relative orientations of the functional groups in the molecule are possible) [6]. The trans isomer has been the target of several in vivo pharmacology studies and was detected twice by the EU EWS (all other detections do not differentiate between isomers).

The compound has a different molecular structure from AH-7921 but the same molecular mass. For this reason, U-47,700 can be mistaken for AH-7921 in a sample if mass spectrometry is the only analytical technique used [1,6-7]. A number of additional techniques can be used to detect U-47,700 such as GC-NPD, GC-MS, U/HPLC-DAD, LC-MS/MS, QTOF-MS, GC-IRD, HR-MS, NMR and UV-Vis. Comparative analysis and the use of a pure reference standard are also likely useful.

U-47,700 may not be a part of routine toxicological screening in death investigations and may require additional testing [6,7].

8. Pharmacology and toxicology

U-47,700 is an opioid analgesic which exhibits “morphine-like pharmacological properties” [8]. It is reported to be 7.5 fold more potent than morphine in animal pain models [8,9].

U-47,700 is a selective μ -opioid receptor agonist ($K_d = 5.3$ and 910 nM for μ and κ -opioid receptors respectively) [9]. In mice, it has been found to have antinociceptive properties (tail flick $ED_{50} = 0.2$ mg/kg, tail pinch $ED_{50} = 0.2$ mg/kg, HCl writhing $ED_{50} = 0.2$ mg/kg), sedative properties (inclined screen $ED_{50} = 9$ mg/kg), morphine antagonism ($ED_{50} > 100$ mg/kg), and gross behavioural (narcotic stimulation) action [8-11].

U-47,700 has not been studied on humans, however limited data from self-reported user experiences suggests it may have abuse liability and dependence potential. Reported subjective effects are similar to other opioids and include euphoria and a strong urge to re-dose [12]. Effects have been reported to last between 60 to 90 minutes which is a shorter duration of action compared to morphine.

Because of its activity at the μ -opioid receptor, adverse effects associated with U-47,700 are likely to be similar to those expected for other opiates and may include respiratory depression. It is believed that naloxone will have the same reversal effect as it does for morphine, fentanyl and other synthetic opioids.

9. Epidemiology

What is the availability of U-47,700 on the drug market?

Monitoring of the surface web conducted in June 2016 has identified vendors selling U-47,700 in bulk (kilogram) and retail quantities. The substance is typically advertised as a 'research chemical' and offered as a powder. Chemical companies based in China appear to be the main producers; this finding is supported by seizures that originated in China (Section 4). U-47,700 is not a controlled substance in China. Websites based in Europe have also been identified selling this substance to consumers.

In addition, U-47,700 has been detected in three different designs of counterfeit diazepam tablets that were seized by police in Scotland, United Kingdom between January and March 2016. During this period, a total of 2,629 tablets were seized (Figure 1). While information on the relative amount of U-47,700 in these tablets is not available, such tablets may pose serious risks as users will not be aware that they are using a potent opioid. It is not known if the presence of U-47,700 in these tablets was deliberate or accidental.

Who uses U-47,700 and why?

There is no data on the prevalence of use of U-47,700. Given its pharmacology, U-47,700 may be actively sought by those looking for substitutes for opioids [1], who may include individuals who use illicit opioids, such as heroin and/or prescription opioids. U-47,700 can be snorted, inhaled ('chasing the dragon'), insufflated (using a nasal spray, for example), taken orally (as tablets) and injected.

At least 15 deaths associated with U-47,700 have occurred in 2015 the USA, some of which with simultaneous post-mortem detections of fentanyl and fentanyl derivatives [7].

10. Additional information

Further information on this substance is available on the EDND profile:

https://ednd.emcdda.europa.eu/html.cfm/index7246EN.html?SUB_ID=482&detail

11. Acknowledgements

The Swedish National Board of Forensic Medicine, ROAR Forensics UK, Eurofins Forensics Belgium, the Laboratory of Medicinal Chemistry of Ghent University, and the Department of Pathology and Forensic Medicine at AZ Damiaan Hospital are thanked for the information on serious adverse events. Colleagues at the corresponding national early warning system are also thanked for their timely reporting. The Scottish Police Authority, Forensic Services in Gartcosh is thanked for the pictures in Figure 1. Drs. Barry Logan and Josh Yohannan are thanked for helpful discussions on this topic.

12. Attachments

This email contains 1 attachment containing a printer-friendly (.pdf) version of this alert

13. References

- 1) Coopman et al. A case of acute intoxication due to combined use of fentanyl and 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide (U-47,700), *Forensic Sci Int.* 2016; 266:68-72;
- 2) Police Scotland, Drug Trend Bulletin, Issue 8, march 2016
<http://www.lanarkshirehivandhepatitis.org/resources/files/news/2016/Police%20Scotland%20Drug%20Trend%20Bulletin%20-%20Issue%208.pdf>
- 3) Police Scotland, Drug Trend Bulletin, Issue 9, may 2016
<http://www.lanarkshirehivandhepatitis.org/resources/files/news/2016/Police%20Scotland%20Drug%20Trend%20Bulletin%20-%20Issue%209.pdf>
- 4) Szmuszkowicz, J. Analgesic n-(2-aminocycloaliphatic)benzamides; US Patent US 4098904 A, The Upjohn Company (Kalamazoo, MI), 1978,
<http://www.google.com/patents/US4098904>
- 5) Report on the risk assessment of 3,4-dichloro-N-{{1-(dimethylamino)cyclohexyl}methyl}benzamide (AH-7921) in the framework of the Council Decision on new psychoactive substances EMCDDA, Lisbon, May 2014,
<http://www.emcdda.europa.eu/publications/risk-assessment/AH-7921>
- 6) Elliott, S. et al. The first reported fatality associated with the synthetic opioid 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide (U-47700) and implications for forensic analysis, *Drug Test Anal.* 2016 doi: 10.1002/dta.1984. [Epub ahead of print]
- 7) Logan, B et al. Case reports of designer opioids in post-mortem forensic toxicology casework; Abstracts IV International Conference on Novel Psychoactive Substances (NPS), Budapest, 30-31 May, 2016.

8) Cheney et al. Factors affecting binding of trans-N-[2-(methylamino)cyclohexyl]benzamides at the primary morphine receptor; J. Med. Chem. 1985; 28(12):1853–64.

9) Loew, G. et al. Structure activity studies of two classes of beta-amino-amides: The search for kappa-selective opioids. NIDA Res Monogr; 1988; (90) 144-151.

10) Szmuszkowicz, J et al. Phenanthridone Analogs of the Opiate Agonist U-47,700 in the trans-1,2-Diaminocyclohexane Benzamide Series. J. Med. Chem. 1982; 25(10): 1125-26;

11) Freeman, M. et al. Naphtho and benzo analogs of the kappa opioid agonist trans-(+)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidiny)cyclohexyl]benzeneacetamide. ; J. Med. Chem. 1991, 34(6):1891-96.

12) Reddit Research Chemicals 'U-47700 addiction and withdrawal' thread. Available at: https://www.reddit.com/r/researchchemicals/comments/43023f/u47700_addiction_and_withdrawal/. Accessed 07 June 2016.

----- ENDS -----

--



Rita Jorge, PhD

Scientific analyst

Action on new drugs sector — Supply reduction and new drugs unit

Tel. (351) 211 21 02 10

**European Monitoring Centre for Drugs and Drug
Addiction (EMCDDA)**

Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal • www.emcdda.europa.eu