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Presidenza del Consiglio dei Ministri

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UNIVERSITÀ DI ROMA

Istituto Superiore di Sanità

Sistema Nazionale di Allerta Precoce
Unità Operativa di Biotossicologia

Dipartimento SAIMLAL
Unità di Ricerca di Tossicologia Forense
Responsabile: prof. Enrico Marinelli

UoFT
Unit of Forensic Toxicology
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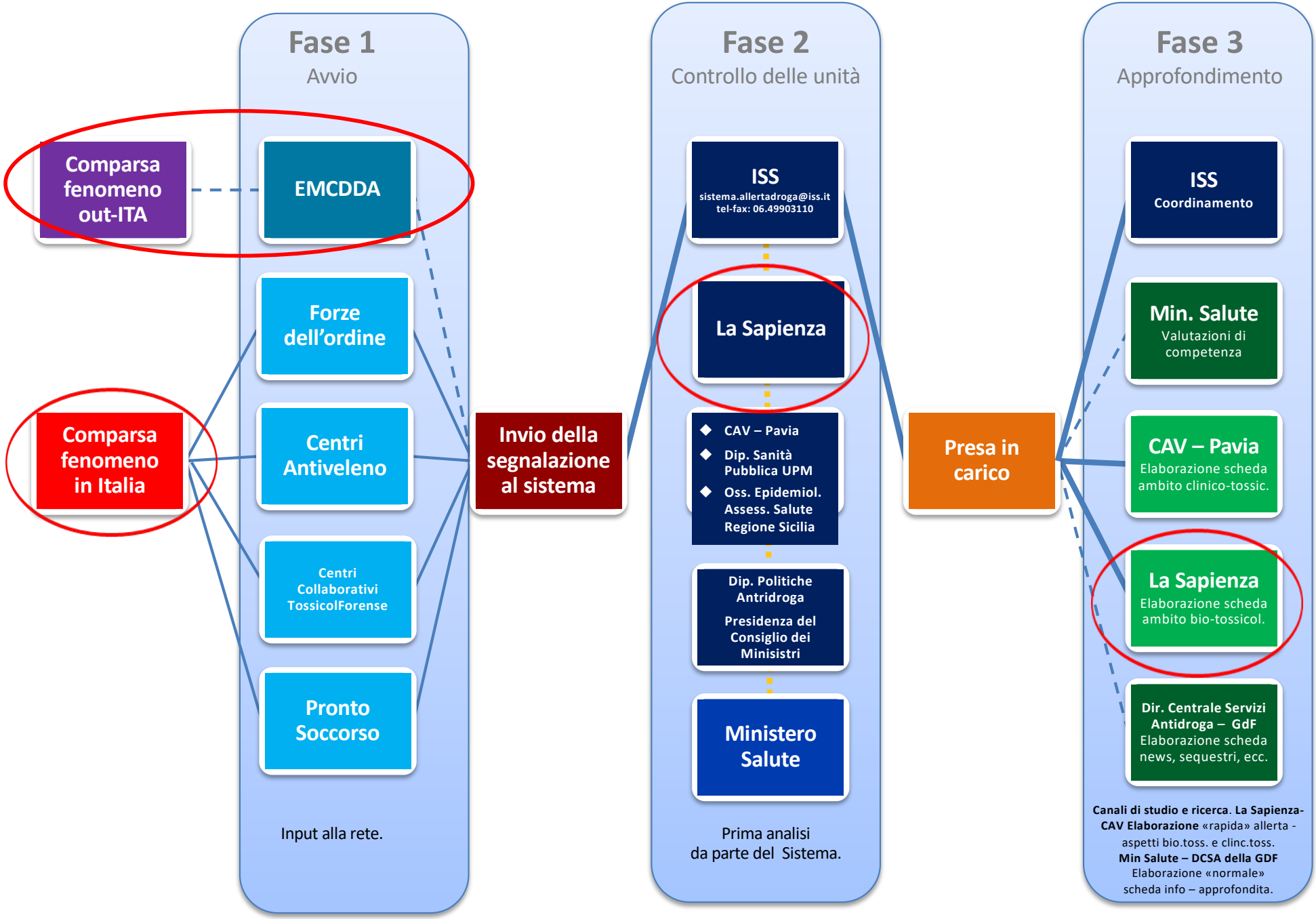
SNAP
SISTEMA NAZIONALE ALLERTA PRECOCE


Fase 1
Avvio
Comparsa fenomeno out-ITA
EMCDDA
Forze dell'ordine
Comparsa fenomeno in Italia
Centri Antiveleno
Centri Collaborativi TossicolForense
Pronto Soccorso
Input alla rete.
Invio della segnalazione al sistema
Fase 2
Controllo delle unità
ISS
sistema.allertadroga@iss.it
tel-fax: 06.49903110
La Sapienza
CAV – Pavia
Dip. Sanità Pubblica UPM
Oss. Epidemiol. Assess. Salute Regione Sicilia
Dip. Politiche Antidroga
Presidenza del Consiglio dei Minisistri
Ministero Salute
Prima analisi
da parte del Sistema.
Presa in carico
Fase 3
Approfondimento
ISS
Coordinamento
Min. Salute
Valutazioni di competenza
CAV – Pavia
Elaborazione scheda ambito clinico-tossic.
La Sapienza
Elaborazione scheda ambito bio-tossicol.
Dir. Centrale Servizi Antidroga – GdF
Elaborazione scheda news, sequestri, ecc.
Canali di studio e ricerca. La Sapienza-CAV Elaborazione «rapida» allerta - aspetti bio.toss. e clinc.toss.
Min Salute – DCSA della GDF
Elaborazione «normale» scheda info – approfondita.

EU EARLY WARNING SYSTEM ALERT

Date:	23/08/2017	RCS ID:	EU-EWS-RCS-AL-2017-0004
Issued by:	EMCDDA	Transmitted by:	Rita Jorge
Recipients:	National Early Warning System Correspondents (National Focal Points)		
Subject:	**Deaths associated with cyclopropylfentanyl — Sweden, June–August 2017**		

1. Information

In the past few years there has been a large increase in the availability of new opioids in Europe. This includes derivatives of the narcotic analgesic fentanyl, known as 'fentanils'. New opioids are sold and used as substitutes for illicit opioids and prescription opioids, sometimes without the knowledge of the users who may believe they are taking other substances. An increasing number of serious harms, including deaths, have been associated with these substances.

The subject of this alert is **cyclopropylfentanyl** (*N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidyl]cyclopropanecarboxamide), a fentanil which has recently been detected in deaths in Sweden.

Given its structural similarity to fentanyl and limited data from an animal study, cyclopropylfentanyl is expected to act as a **narcotic analgesic** [1]. The effects of such substances include euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia and respiratory depression. Cyclopropylfentanyl is also likely to have an abuse liability and dependence potential.

Cyclopropylfentanyl was **formally notified** in August 2017 on behalf of Latvia. The notification was related to a seizure of a small amount of white powder (0.0345 g) by police on 25 July. No other seizures or collected samples have been reported to the EMCDDA.

Since the formal notification, Sweden has reported **22 deaths with confirmed exposure** to cyclopropylfentanyl. The deaths occurred between June and August 2017. A range of other substances were detected in most of the deaths, including other opioids in at least 8 cases. These included morphine, methadone, buprenorphine and U-47,700. In most of cases, the cause of death has not yet been reported as the deaths are still under investigation. In at least 6 cases, cyclopropylfentanyl caused or contributed to the death.

At present there is no further information regarding the supply of cyclopropylfentanyl in Europe. In Georgia, United States, cyclopropylfentanyl was associated with an outbreak involving more than 40 overdoses, 5 of which fatal, in a two-week period in June 2017. The substance was identified with U-47,700 in counterfeit Percocet tablets [2, 3].

Similar to other fentanils, the most serious acute health risk from using cyclopropylfentanyl is likely to be respiratory depression, which in overdose could lead to apnoea, respiratory arrest, and death [4–8]. The acute health risks associated with cyclopropylfentanyl may be exacerbated by: the difficulty in diluting the substance which may be active and potentially fatal in small amounts; a lack of experience with its effects and dosing; the use of other central nervous system depressants at the same time (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 poisoning.

The antidote **naloxone** is likely to reverse acute poisoning, including respiratory depression, caused by cyclopropylfentanyl [9, 10]. Recent clinical and community experience in treating poisonings caused by fentanils suggests that higher doses and additional doses (including infusions) of naloxone may be required to fully reverse poisoning in some cases [11–14]. In the recent outbreak in Georgia, involving counterfeit Percocet tablets containing cyclopropylfentanyl and U-47,700 it was reported that in some cases first responders needed to administer larger than normal doses of the antidote naloxone in order to treat the poisoning [3].

2. Data Use Restrictions

If you received this alert as a national early warning system correspondent (NFP), please note that this alert must be restricted to your national early warning system network. Do not make it public. If you have any questions in this respect, please contact the EMCDDA.

If this alert has been sent to you by your national early warning system correspondent (NFP), please direct any questions to them.

If you plan to use the information in this alert as part of a risk communication aimed at users and potential users, please note that a challenge in respect to reducing risk in these groups is the balance between providing information to prevent harm and the unintended consequences of communicating the risks of opioids. There is evidence that using terms to describe opioids as 'potent', 'strong', 'deadly', and 'toxic' can lead some individuals to specifically seek out these substances. Such unintended promotion of the substances may also extend to former users and other groups.

3. Action Required

The EMCDDA requests that you report any additional data you may have on cyclopropylfentanyl so that we can improve our understanding of the potential risks it may pose to Europe. We are particularly interested in analytically confirmed detections of the substance, including those involving serious adverse events. Data should be reported as soon as possible to: ews@emcdda.europa.eu

4. Further Information

Further information on cyclopropylfentanyl is available from:

- EU Early Warning System Formal Notification of *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidyl]cyclopropanecarboxamide (cyclopropylfentanyl) by Latvia as a new psychoactive substance under the terms of Council Decision 2005/387/JHA. EU-EWS-RCS-FN-2017-0029. Issued on 4 August 2017.
- EDND: https://ednd.emcdda.europa.eu/html.cfm/index7246EN.html?SUB_ID=676&detail

EDND – European information system and database on new drugs

Search | Advanced search

Substances | Reporting forms | Reports | Search EDND | Alerts | Trainings | Meetings | Announcements | Analytical databank | Miscellaneous

EDND > Substances

Current user: pacifro | Logout

Substances

Substance: Cyclopropylfentanyl

Created
August 2017

Updated
August 2017

Type
Narcotic drugs

Group
Opioids

Name
Cyclopropylfentanyl

Nature of substance
Cyclopropylfentanyl is a phenylpiperidine and a derivative of fentanyl. It differs from fentanyl due to the presence of the cyclopropane moiety in place of the ethyl linked to the carboxamide. Cyclopropylfentanyl is also structurally related to tetramethylcyclopropanefentanyl, which was formally notified in June 2017.

Cyclopropylfentanyl was originally mentioned in a patent by Janssen in the 1960s. The measured melting point was reported as 119.5 – 120.4 ° C.

Systematic chemical name
N-phenyl-N-[1-(2-phenylethyl)-4-piperidyl]cyclopropanecarboxamide

Other names

Chemical names: N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-cyclopropanecarboxamide, N-(1-phenethylpiperidin-4-yl)-N-phenylcyclopropanecarboxamide

Other names: cyclopropyl fentanyl, cyclopropyl-fentanyl

Alerts

[EU-EWS-RCS-AL-2017-0004] Deaths associated with cyclopropylfentanyl — Sweden, June–August 2017
(Last Update: 29/08/2017)

Reports to EMCDDA

Sweden (Reporting Form): On 23 August 2017 the Swedish FP reported a seizure of 3ml liquid seized on 07.07.2017 by the Police at Trollhättan. The structure has been identified using a reference standard from Cayman Chemicals [CAY-21739] and GC-MS and GC-IRD analysis at the Swedish National Forensic Centre (NFC).

Not country-specific or non-EU country (Reporting Form): Formal notification of N-phenyl-N-[1-(2-phenylethyl)-4-piperidyl]cyclopropanecarboxamide (cyclopropylfentanyl) by Latvia as a new psychoactive substance under the terms of Council Decision 2005/387/JHA, 4 August 2017.

Latvia (Reporting Form): On 3 August 2017 the Latvian FP reported a seizure of 0.0345 grams of white powder seized by the Police of Latvia, in Riga, on 25 July 2017. The substance was analytically confirmed by GC-MS by the Forensic service department of the State Police, which was compared with the Cayman Spectral Library.

Information from international partners

Information from EMEA
.

Information from other partners / institutions / countries
.

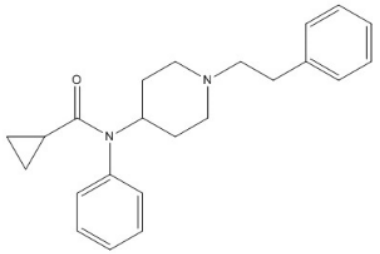
Assessment status in the UN system
.

Other chemical names and variants
N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-cyclopropanecarboxamide
N-(1-phenethylpiperidin-4-yl)-N-phenylcyclopropanecarboxamide

Chemical Abstracts Service (CAS) registry number
1169-68-2

Molecular information

Molecular structure:



Molecular formula: $C_{23}H_{28}N_2O$

Molecular weight: 348.49

Identification and analytical profile
.

cyclopropylfentanyl_LV.jpg
Kindly provided by the Latvian FP.

Synthesis, manufacture and precursors
.

Physical description
.

Uses & Risks

Modes and scope of the established or expected use
.

Health risks

Pharmacology and toxicology

There is currently limited information available on the pharmacology and toxicology of cyclopropylfentanyl. Due to its structural similarity to fentanyl, it is expected to have opioid narcotic analgesic effects. Data from a review studying the chemical anatomy of potent morphine-like analgesics, suggests cyclopropylfentanyl can reduce signs of experimentally-induced pain in rodents to a similar extent as fentanyl (Table 2.13).

In June 2017, cyclopropylfentanyl was identified with U-47,700 in counterfeit Percocet tablets in Central Georgia, United States. Over a two week period, these tablets were associated with an outbreak involving more than 40 overdoses, 5 of which were fatal. It was also reported that in some cases, first responders needed to administer larger than normal doses of the antidote naloxone in order to treat the poisoning.

Social risks

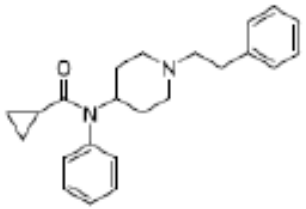
Allegato A

Spettro di massa ottenuto dalla Biblioteca Cayman Spectral

Nome:

CICLOPROPILFENTANIL

Struttura molecolare:



Formula di struttura:

$C_{23}H_{28}N_2O$

Numero CAS:

non disponibile

Nome IUPAC:

N-Fenil-N-[1-(2-Feniletil)-4-piperidil]ciclopropanecar

Altri nomi:

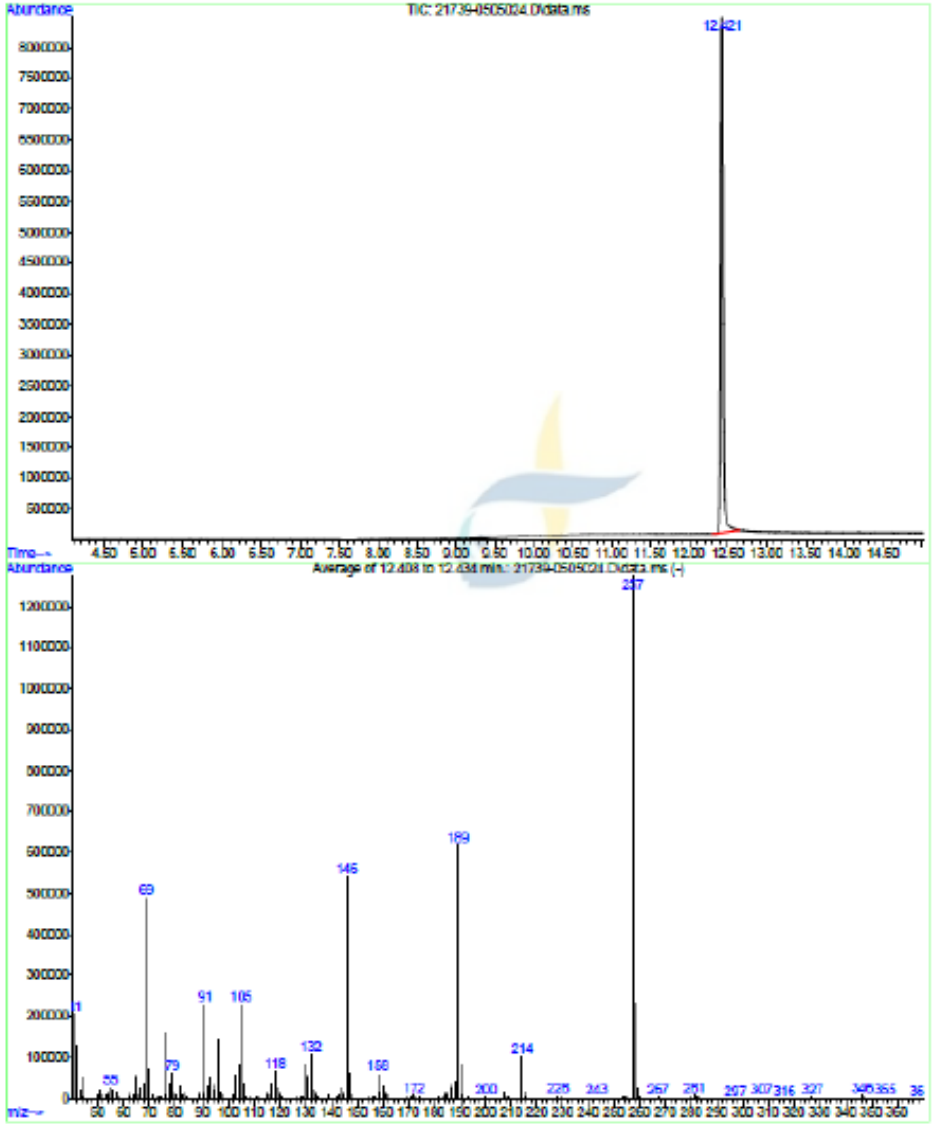
N-fenil-N-[1-(2-feniletil)-4-piperidinil]-ciclopropancar
fenilciclopropancarbossamide.

Peso molecolare:

378.9 g/mol

Aspetto:

Polvere, compresse, liquida (spray o carta imbevuta



polvere bianca sequestrati dalla polizia della

C-MS dal Dipartimento Forense della Polizia
yman Spectral.

di fentanil. Si differenzia da fentanil per la
egato alla carbossamide. Il Ciclopropilfentanil
ntanil, che è stato formalmente notificato nel

retto da Janssen negli anni '60 [1]. Il punto di

icologia e la tossicità del ciclopropilfentanil. A
ssono ipotizzare effetti analgesico-narcotici. I
potenti suggerisce che ciclopropilfentanl può
in misura analoga a quella del fentanil [2].

e Tabelle del D.P.R. 309/90 e s.m.i

NV, assignee. N-(1-alkyl-4-piperidyl)-N-
1517671 (A). 1968 March
alDocument?CC=FR&NR=1517671A&KC=A
EP#

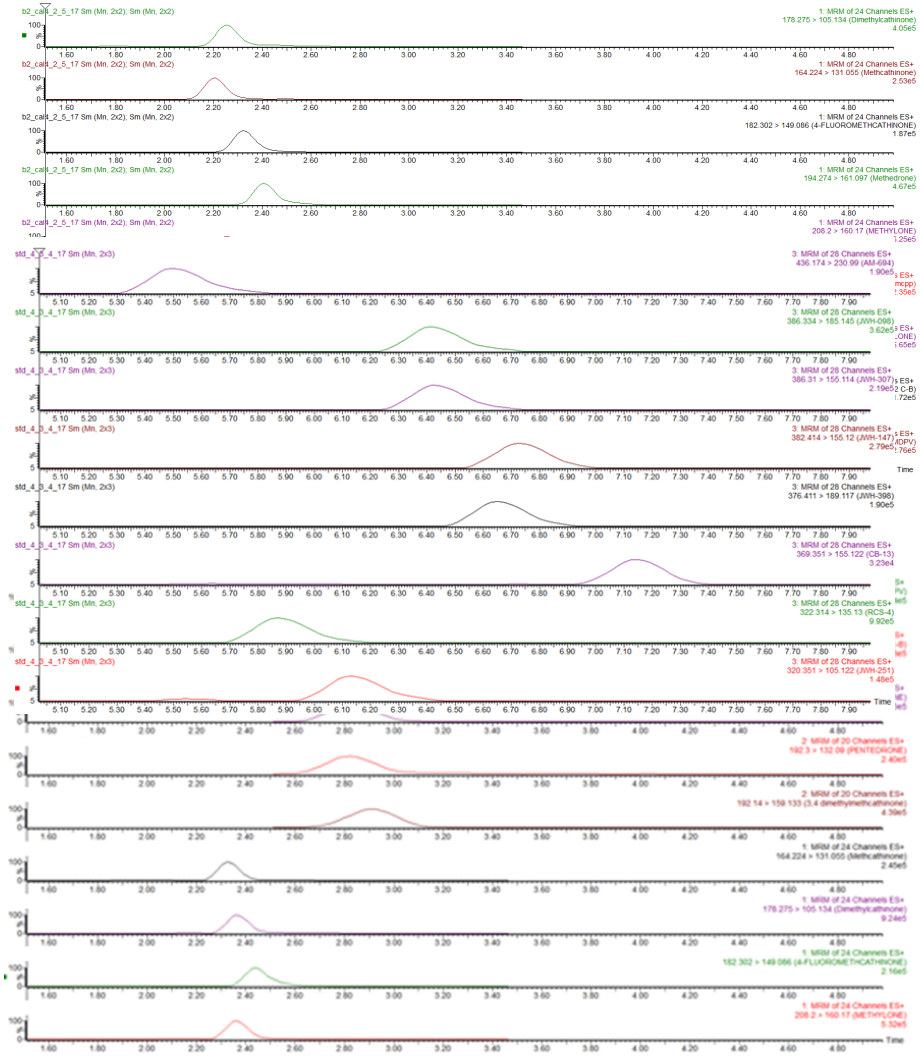
omy of potent morphine-like analgesics. In A
/ol. 2, 1968, pp. 25-60, Marcel Dekker, Inc.,
http://dx.doi.org/10.1002/jps.2600570852

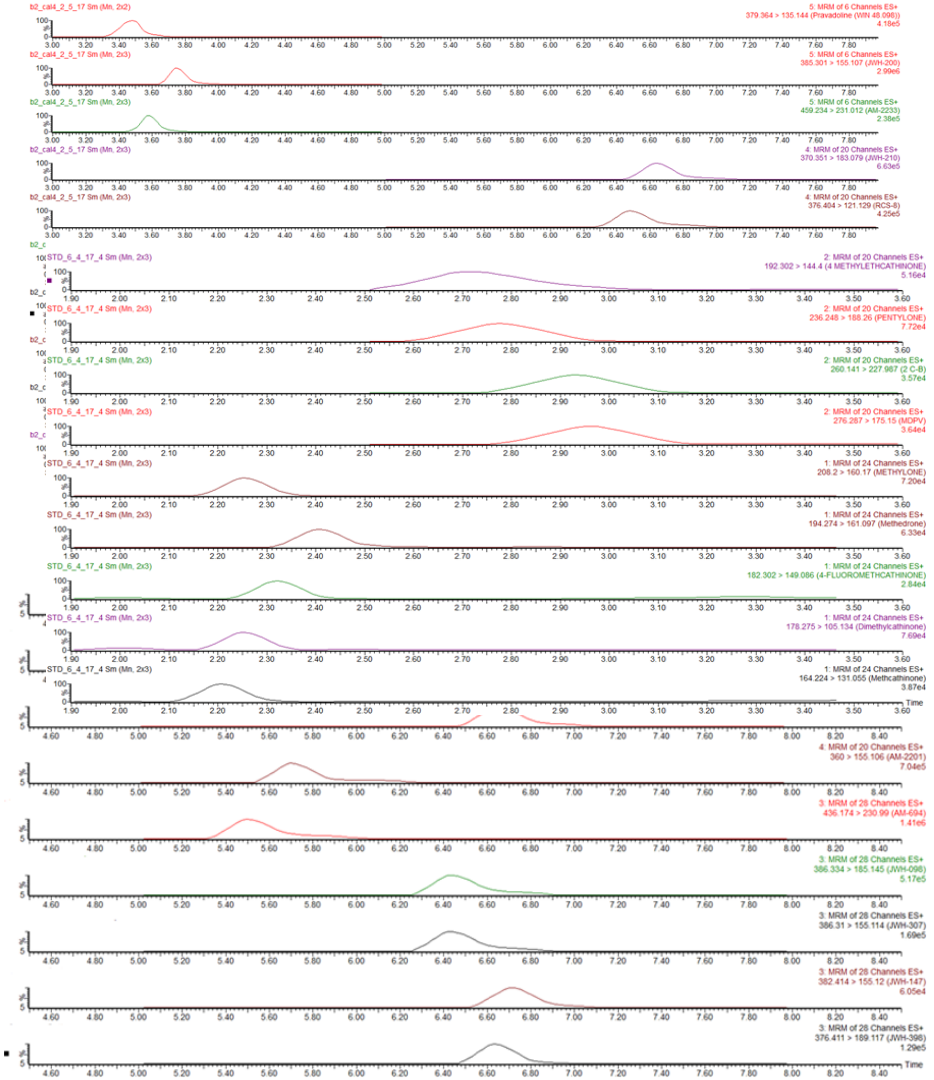
METHOD DEVELOPMENT AND VALIDATION FOR THE DETERMINATION OF 49 NEW PSYCHOACTIVE SUBSTANCES (NPS) IN SERUM, URINE AND HAIR BY ULTRA-HIGH PERFORMANCE LIQUID CHROMATOGRAPHY - TANDEM MASS SPECTROMETRY (UHPLC-MS/MS): APPLICATION TO REAL SAMPLES.

Doctoral thesis of Christalla Kiriakou from Cyprus codirected by Dr. Roberta Pacifici and Prof. Enrico Marinelli

49 NPS belonging to different chemical classes (synthetic cannabinoids, synthetic cathinones, benzofurans, aminoindanes, phenethylamines, piperazines, piperidines) in serum, urine and hair extracts in a single run, following rapid and easy sample pre-treatment.

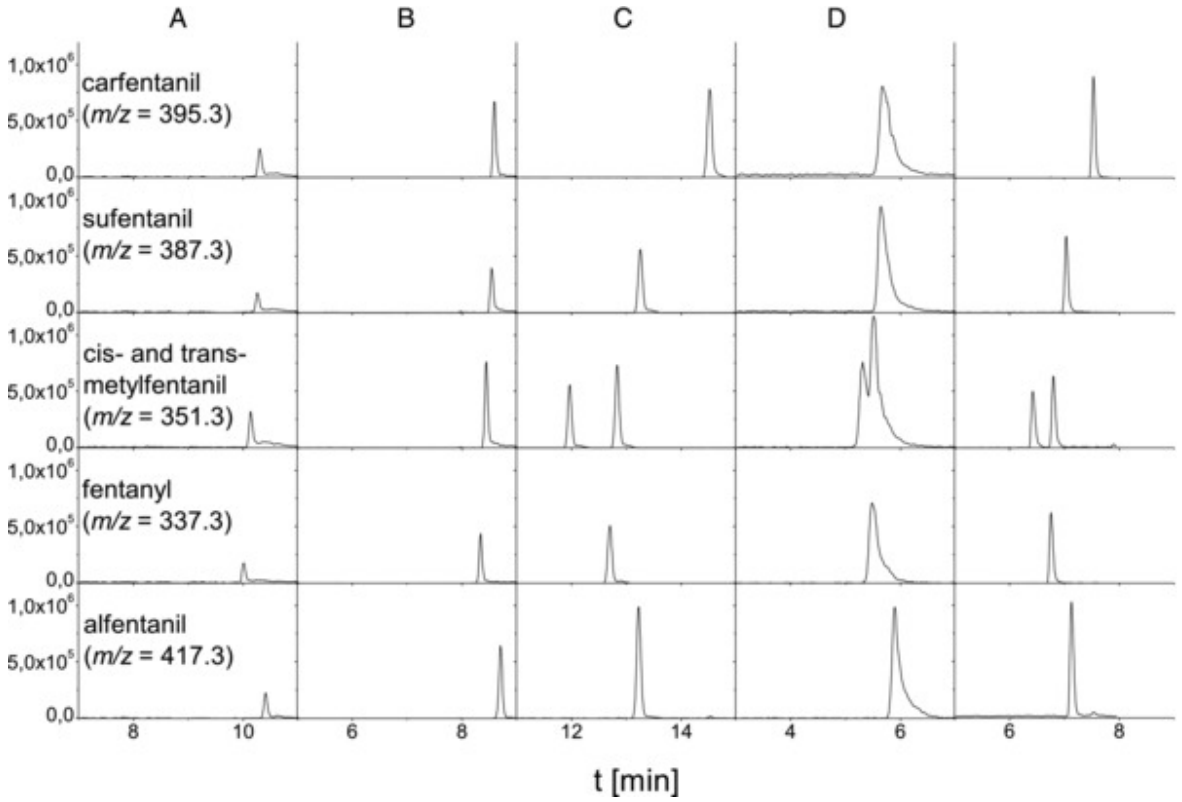
The method was very fast, easy to perform, cheap and minimum amount of sample (0.1 ml serum or urine and 50 mg hair) was required. Chromatography was carried out using an Acquity UPLC BEH reversed phase C18 column (2.1 x 75 mm, 1.7 µm) and a gradient elution with two solvents: 0.1% formic acid in water (solvent A) and acetonitrile (solvent B). The separated analytes were detected with a triple quadrupole mass spectrometer operated in multiple reaction monitoring (MRM) mode via positive electrospray ionization (ESI).





Determination of illegal fentanyl derivatives in non biological and biological matrices

Emilia Marchei, Enrico Marinelli, Simona Pichini, Francesco Paolo Busardò, Roberta Pacifici



Invited Review on Trends in Analytical Chemistry

UHPLC-MS/MS assay of most recent illegal fentanyl derivatives in non biological and biological matrices

Emilia Marchei, Roberta Pacifici, Enrico Marinelli, Giulio Mannocchi, Francesco Paolo Busardò, Simona Pichini

FENTANYL

FENTANYL-D5

ACETYL-FENTANYL

CARFENTANIL

BUTYRILFENTANIL

CYCLOPROPILFENTANYL

4 FLUOROBUTYRFENTANYL

FURANYLFENTANYL

ACRYLFENTANYL
NORFENTANYL

ACETYL NORFENTANYL