New Pchysoactive Substances

Un desafio para los laboratórios de Toxicología Forense

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EUDA
EUROPEAN UNION DRUGS AGENCY

New psychoactive substances (NPS)

- **A new psychoactive substance (NPS)** is defined as 'a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions'

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- Actualmente han sido detectadas ***1258*** NPS a nivel mundial (UNODC – Early Warning Advisory / https://www.unodc.org/lss/home/nps)

- Como controlar un número tan elevado de substancias en un mercado tan dinámico?

  - ✓ Acceso a la información?
  - ✓ Preocupaciones actuales. Cuales son las substâncias mas "populares"?
  - ✓ *Target screening* (LCMSMS) vs *Unknown* (ToF, Orbitrap)?
  - ✓ Patrones analíticos (cuantos?)
  - ✓ Muestras analizadas?
  - ✓ Sensibilidad analítica?

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❑ ***Acceso a información de referencia***

- UNODC Early Warning Advisory (EWA) Tox-Portal (https://www.unodc.org/tox/#/login)

- EUDA (European Union Drugs Agency (https://www.euda.europa.eu/index_en)

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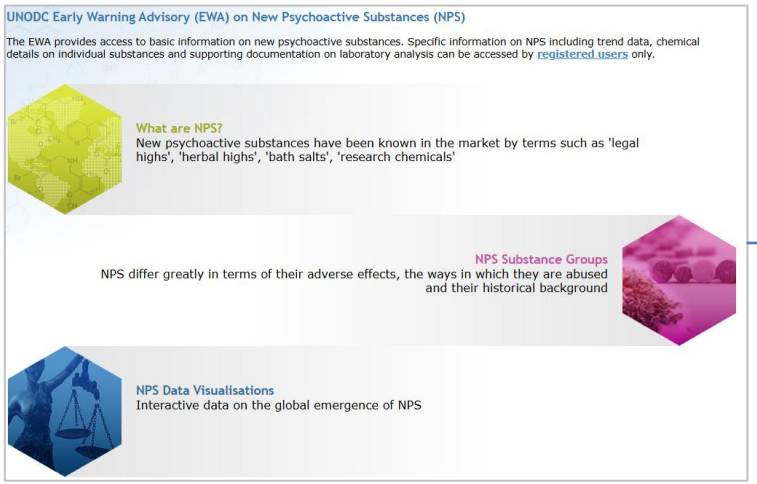

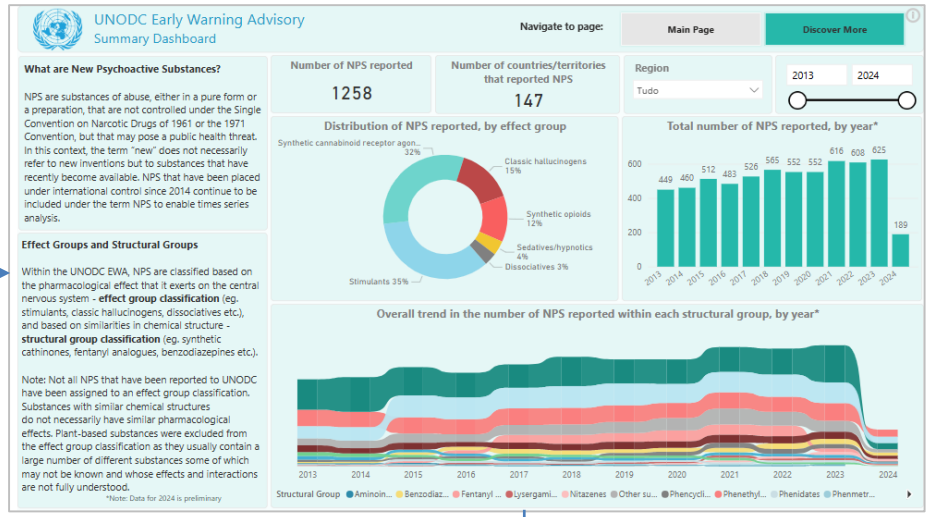

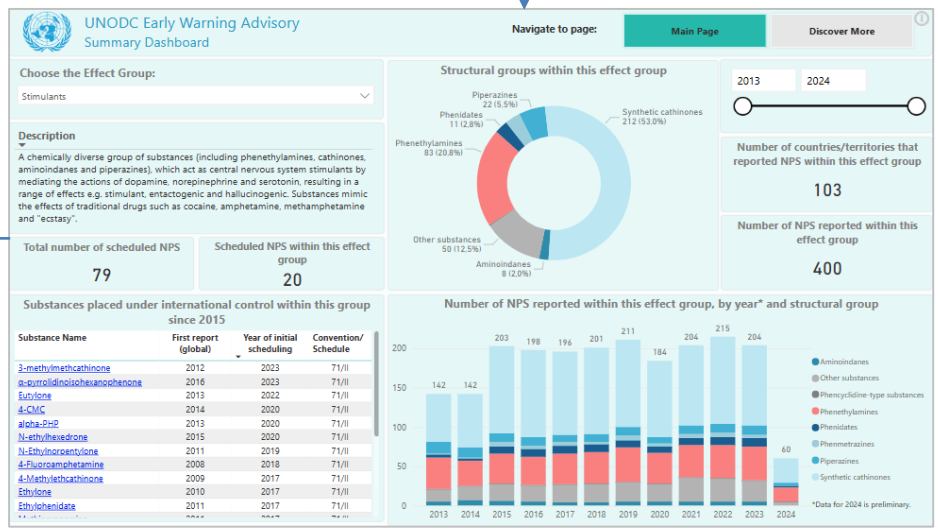

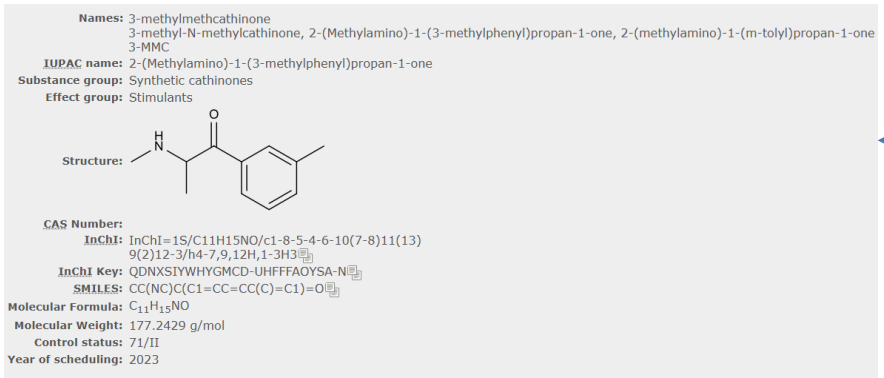

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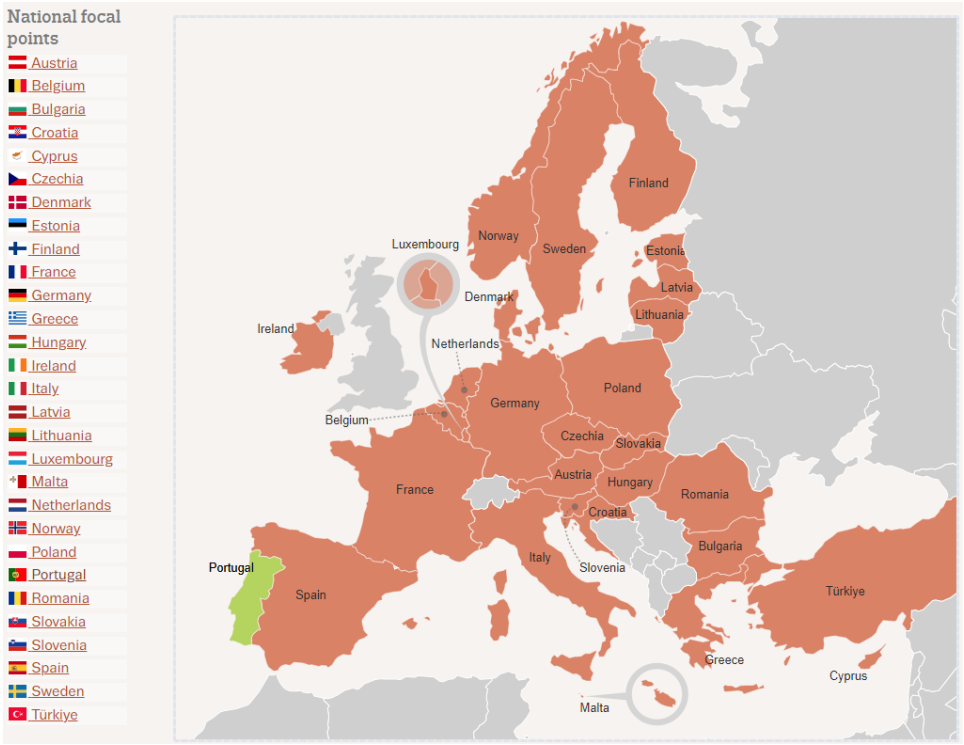
❑ *Acceso a información de referencia*

- EUDA (recolección de datos)

Reitox is the European information network on drugs and drug addiction created at the same time as the EMCDDA (EUDA).

Members of the Reitox network are designated national institutions or agencies responsible for data collection and reporting on drugs and drug addiction. These institutions are called 'national focal points' or 'national drug observatories'.



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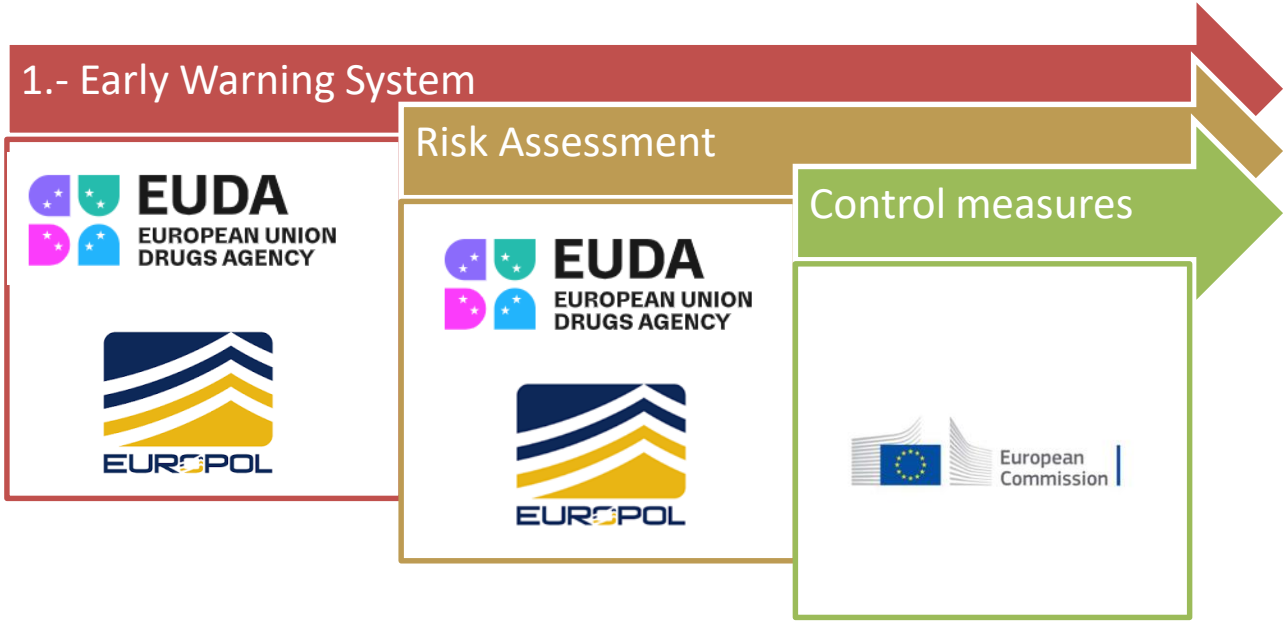
❑ ***Acceso a información de referencia***

- EUDA – *"Three steps legal framework"* (https://www.euda.europa.eu/index_en)



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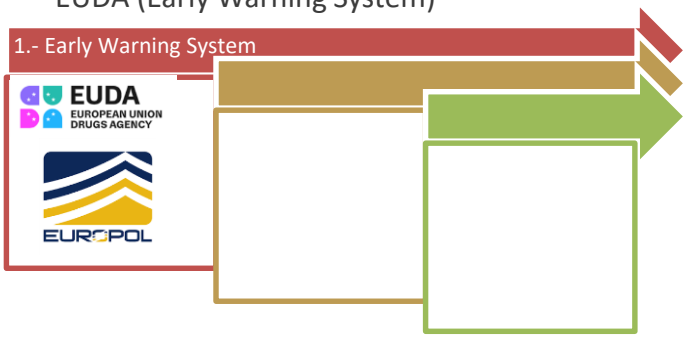
❑ ***Acceso a información de referencia***

- EUDA (Early Warning System)

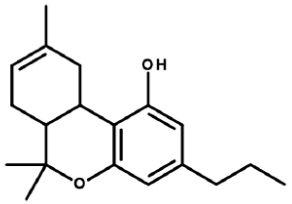


EUDA
EUROPEAN UNION DRUGS AGENCY

EU Early Warning System: Formal Notification

Formal notification of 3-propyl-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (delta-8-THCV) by Sweden as a new psychoactive substance under the terms of Regulation (EU) No 2023/1322 and Council Framework Decision 2004/757/JHA

Date issued	**RCS ID**
30.10.2024	EU-EWS-RCS-FN-2024-0034
Issued by	**Transmitted by**
EUDA	Action on New Drugs Sector, EUDA



Δ8-THCV

Type: Seizure

Case Report identifier: EDND-CR-2024-350

Details: delta-8-THCV and delta-9-THCV were identified in a seizure of a cartridge of 1 ml of yellow E-liquid seized by Danish Customs, in Koege, on 26 September 2023. The material was sent from Czech Republic to Denmark and was contained in a packaging labelled as "Blue Dream THCV 20% THCV 60% CBG, 20% CBN Distillate".

The material contained delta-9-THCV (17%), delta-8-THCV (4%), CBN (21%), CBG (20%) and CBD (21%). The substances were analytically confirmed using GC-MS, LC-MS and HPLC by the Section of Forensic Chemistry, University of Copenhagen.

Details: delta-8-THCV and delta-9-THCV were found in a seizure of 10 g of brown thick liquid seized by Swedish Customs at Sturup airport on 26 October 2023. The material was found in the postal flow, send from Italy to Sweden and was contained in a glass bottle labelled as "D9 THCV 10g" with a handwritten text.

Delta-8-THCV and delta-9-THCV were analytically identified by GC-MS with commercially available reference standards.

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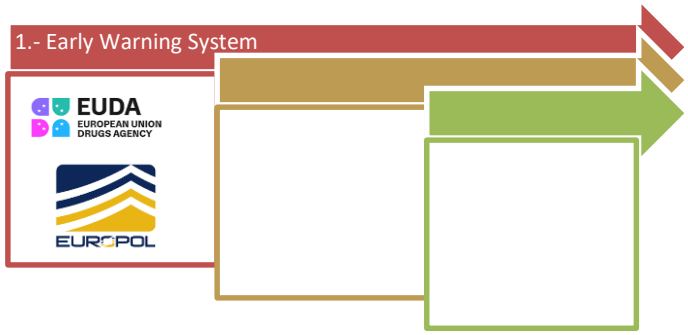
❑ ***Acceso a información de referencia***



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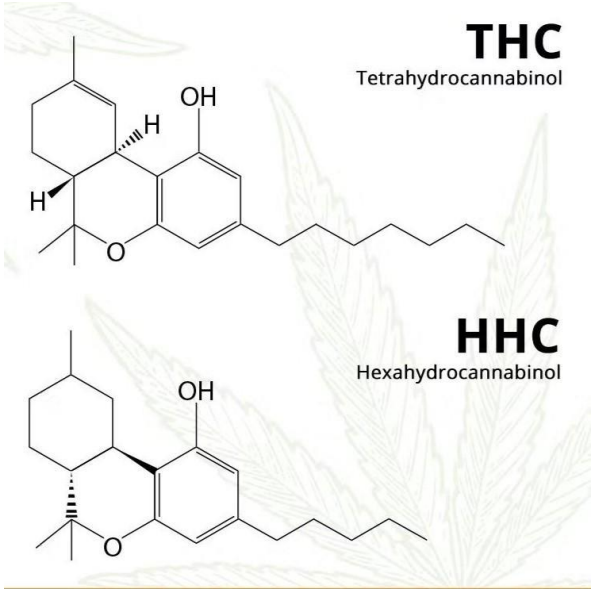


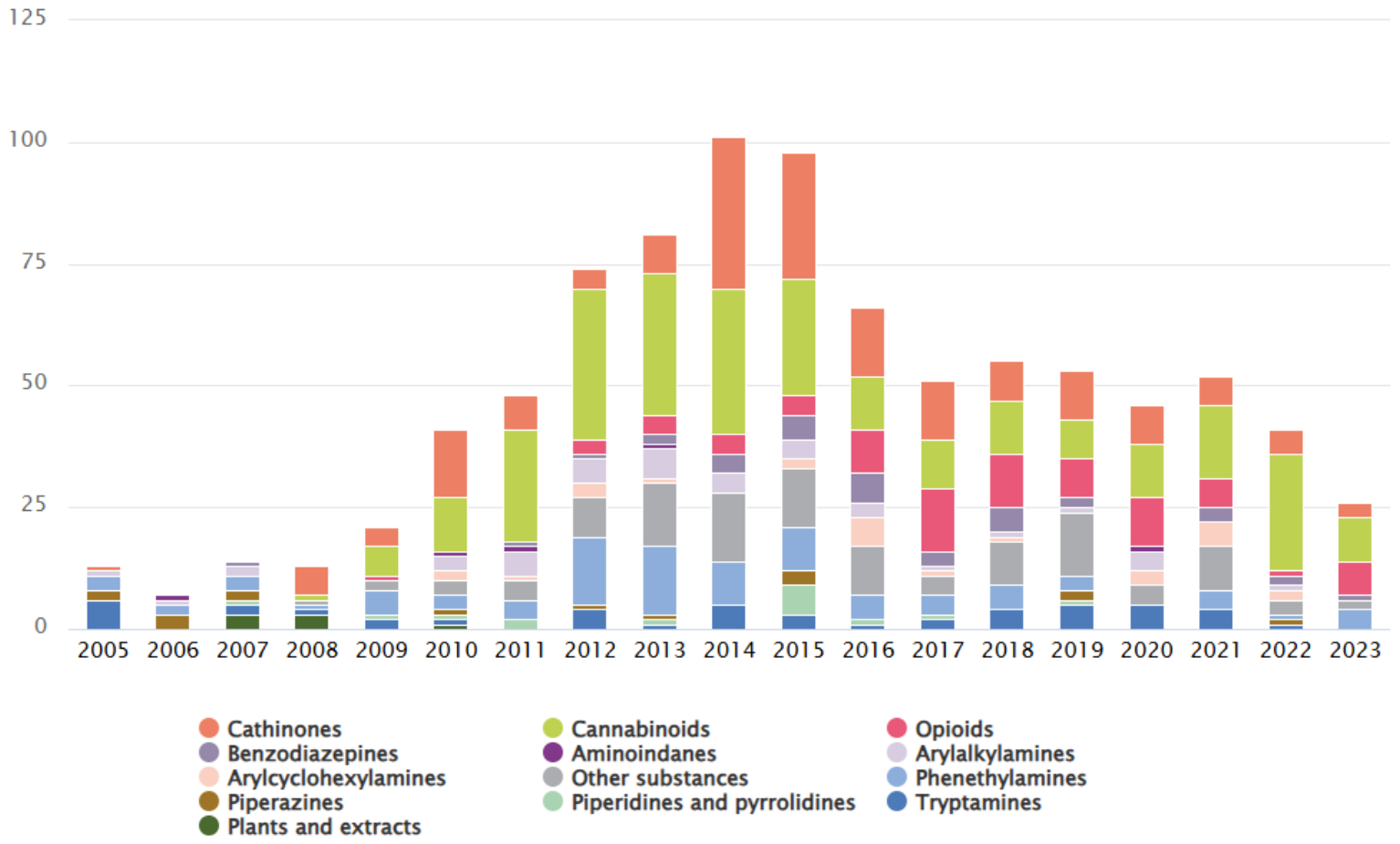
EU Early Warning System: Intensive monitoring

HHC-P-O-acetate under intensive monitoring as of 9 October 2024

Date issued	**RCS ID**
09.10.2024	EU-EWS-IM-2024-0014
Issued by	**Transmitted by**
EUDA	Action on New Drugs Sector, EUDA
Read with	**Recipients**
EU-EWS-RCS-FN-2024-0018	Early Warning System Network

New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

❑ ***Acceso a información de referencia***



Fuente: EUDA (European Drug Report 2024). https://www.euda.europa.eu/publications/european-drug-report/2024_en

New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

❑ ***Acceso a información de referencia***

EMCDDA risk assessments

Since 1997, the EMCDDA has conducted 37 risk assessments on new psychoactive substances. Over 70% of these assessments have been conducted since 2012, which reflects the growth in the market and an increase in harms reported in recent years.

- Risk assessment of 3-MMC (2022)
- Risk assessment of 3-CMC (2022)
- Risk assessment of 4F-MDMB-BICA (2021)
- Risk assessment of MDMB-4en-PINACA (2021)
- Risk assessment of isotonitazene (2020)
- Risk assessment of methoxyacetylfentanyl (2018)

RISK ASSESSMENTS 31

ISSN 1725-4493

Isotonitazene

Report on the risk assessment of *N,N*-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine (isotonitazene) in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended)

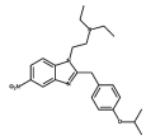
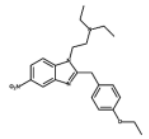
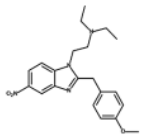
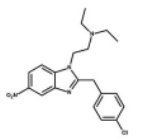
Chemical and physical properties and the methods and precursors used for manufacture

Chemical and physical properties

Isotonitazene belongs to the 2-benzylbenzimidazole group of opioid analgesics. In particular, it is a 5-nitro-2-benzylbenzimidazole derivative. This group also includes the closely related homologues, etonitazene and metonitazene, as well as clonitazene.

Isotonitazene differs from etonitazene and metonitazene in the substitution at the *para*-position of the benzyl moiety, which is an isopropoxy group in isotonitazene, an ethoxy group in etonitazene and a methoxy group in metonitazene. Isotonitazene differs from clonitazene in the replacement of the chloro halogen atom with the ethereal isopropoxy group. The *n*-propoxy isomer, protonitazene, is also known. The chemical structures, molecular formulae and molecular weights of these compounds are provided in Figure 1.

FIGURE 1
Chemical structure, molecular formula and molecular weight of isotonitazene, etonitazene, metonitazene and clonitazene.

Isotonitazene	Etonitazene	Metonitazene	Clonitazene
			
Molecular formula: $C_{23}H_{30}N_4O_3$	Molecular formula: $C_{22}H_{28}N_4O_3$	Molecular formula: $C_{21}H_{26}N_4O_3$	Molecular formula: $C_{20}H_{23}ClN_4O_2$
Molecular weight: 410.51	Molecular weight: 396.48	Molecular weight: 382.46	Molecular weight: 386.88

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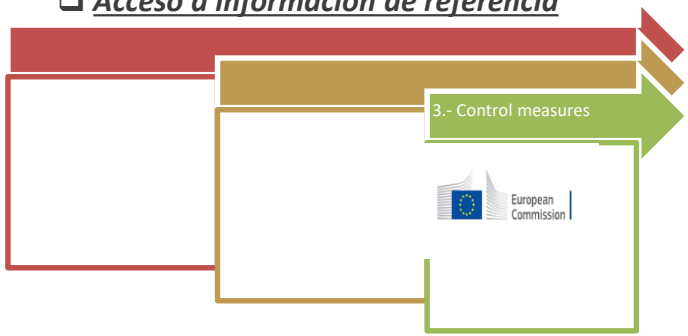
❑ ***Acceso a información de referencia***



News

New psychoactive substances: Commission proposes new ban and strengthens the EU's Early Warning System and risk assessment

31.08.2016

Today, the European Commission has proposed to subject the new psychoactive substance MDMB-CHMICA (sometimes referred to as 'Black Mamba') to control measures across the European Union.

News

Council adopts its position on the reform of the new psychoactive substances legislation

09.12.2016

On 8 December, the Council adopted its position on a package reforming the legislation on new psychoactive substances (NPS).

New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

❑ ***Preocupaciones actuales***

- **Canabinóides:**

a) Sintéticos / Semisintéticos

Ultimamente se han detectado varios casos de intoxicaciones (algunas de ellas letales) provocadas por el consume de canabinóides semisintéticos como el **HHC (Hexahidrocannabinol)** y **Δ8-THC**. También se han detectado canabióides semisintéticos en alimentos del tipo “jelly gummies”.

Sweets containing the synthetic cannabinoid 5F-EDMB-PICA seized by Swedish Customs, August-September 2021. Source: Swedish Customs.

Los canabinoides semisintéticos tambiém pueden aparecer como adulterantes en de heroina (Francia/Lituania – 2023)

New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

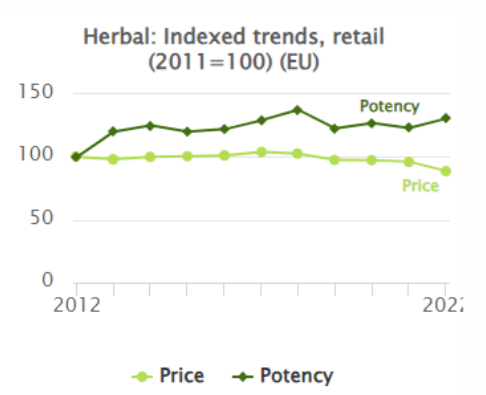
❑ ***Preocupaciones actuales***

- **Canabinóides:**

a) Naturales (THC, CBD)

- *Riesgo de consume inadvertido* -> Canabis natural adulterado con canabinóides sintéticos / semisintéticos.

- *Aumento de la potencia del canabis natural –THC* (cantidad de sustancia psicoactiva presente en cada muestra).



Marihuana (+ 57%)

Resina + 200%

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❑ *Preocupaciones actuales*

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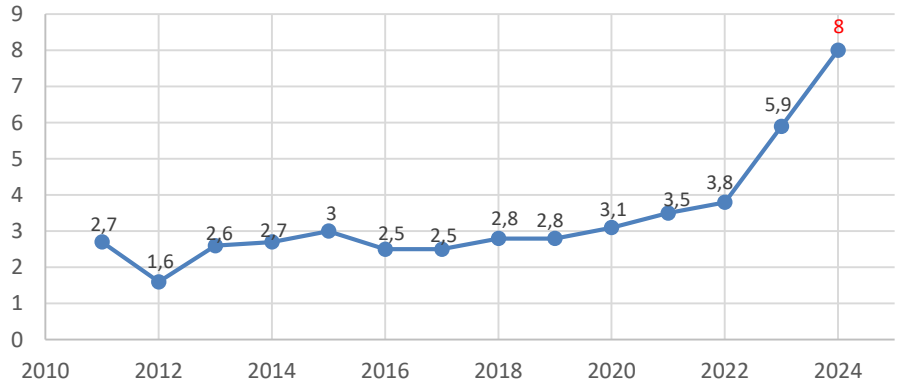
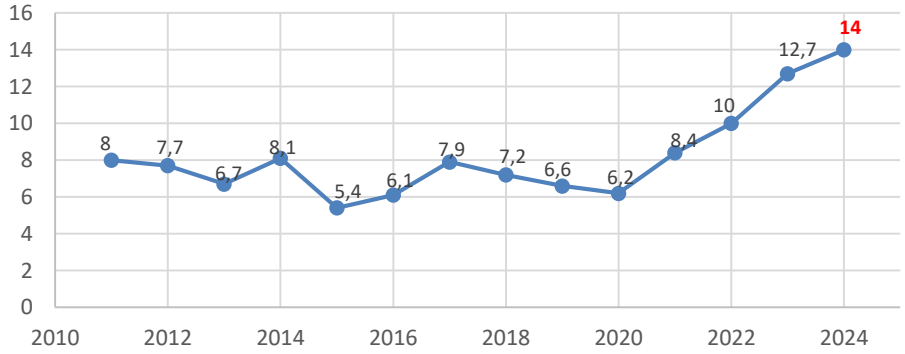
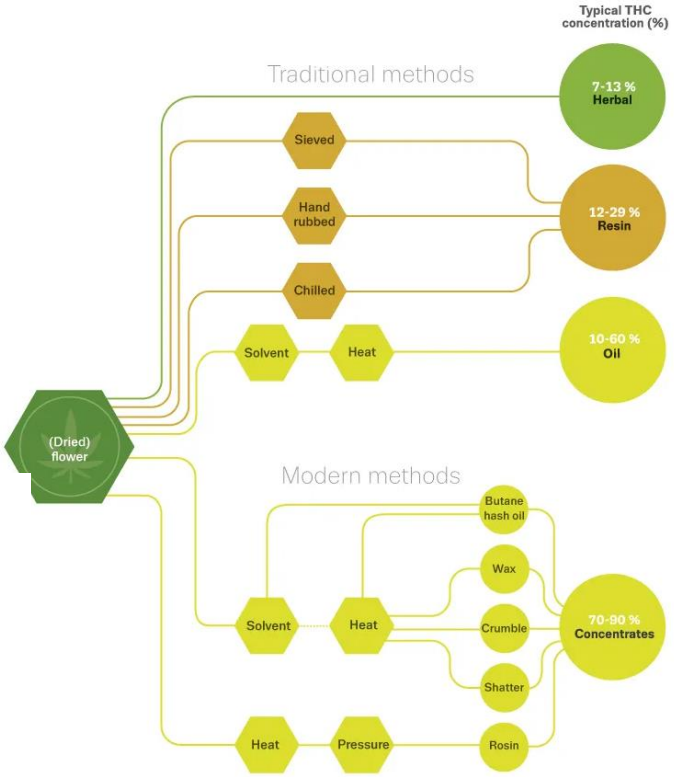


Concentração média (ng/mL) de Δ9-THC (muestras controles de carretera)*



Concentração média (ng/mL) de Δ9-THC (muestras post-mortem)*



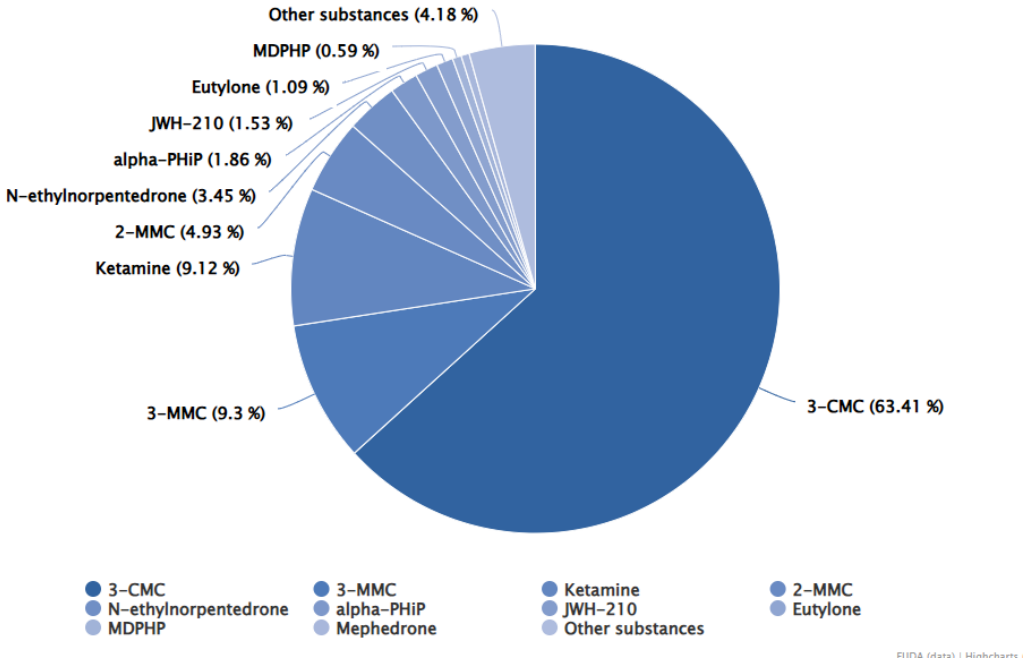
* Muestras analizadas en el laboratório de toxicologia forenses de Lisboa (INMLCF, IP - Portugal

New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

❑ ***Preocupaciones actuales***

- **Catinonas:**
  - Substitutos de anfetaminas en algunos paises de Europa
  - Incautaciones de grandes cantidades de 3-CMC (Chloromethcathinone) y 3-MMC (3-Methylmethcathinone) provenientes de la India indican que estas substancias son bastante ppulares en algunos paises.
  - Algunas catinonas son vendidas como MDMA (como substitutos y como adulterantes)

Incautaciones de NPS en la Unión Europea (2022)



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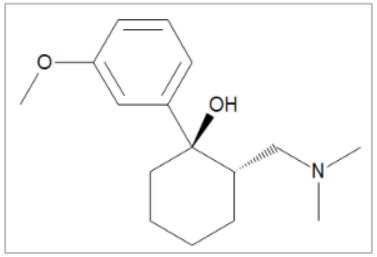
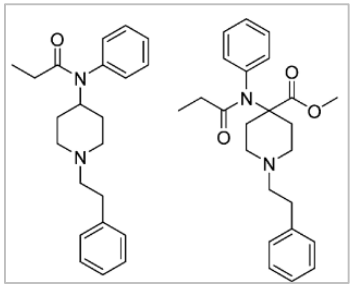
❑ ***Preocupaciones actuales***

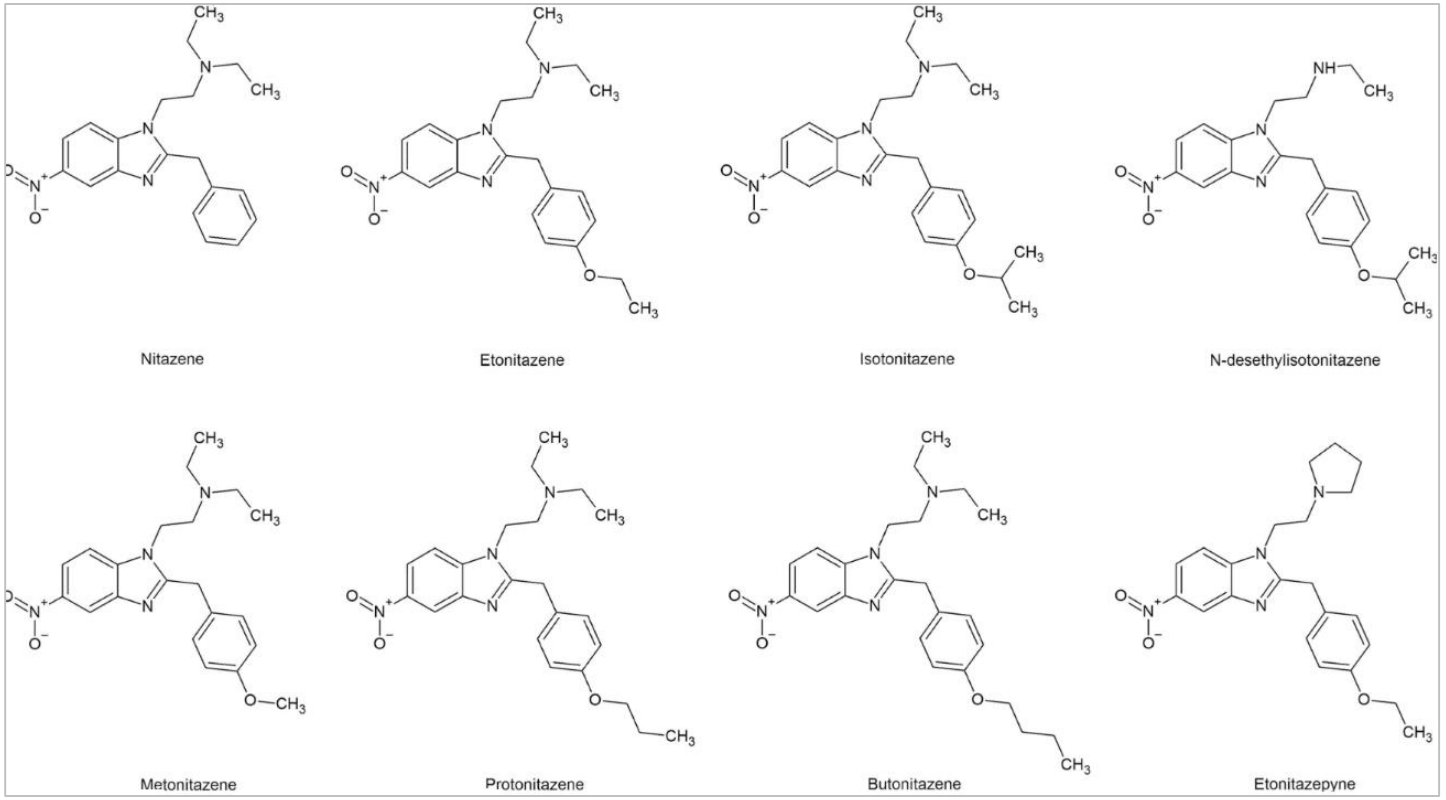
- **Opioides sintéticos:**



Tramadol



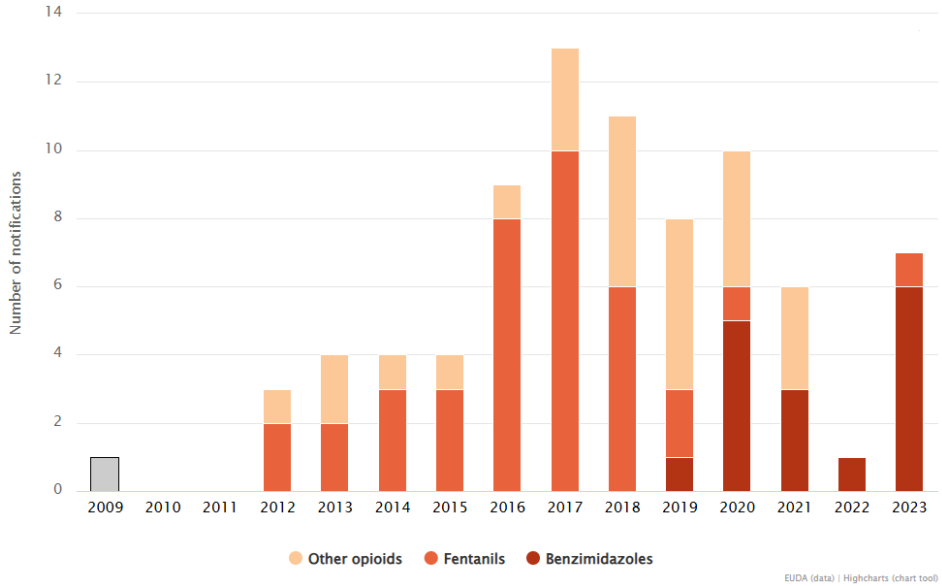
Fentanilo / Carfentanilo

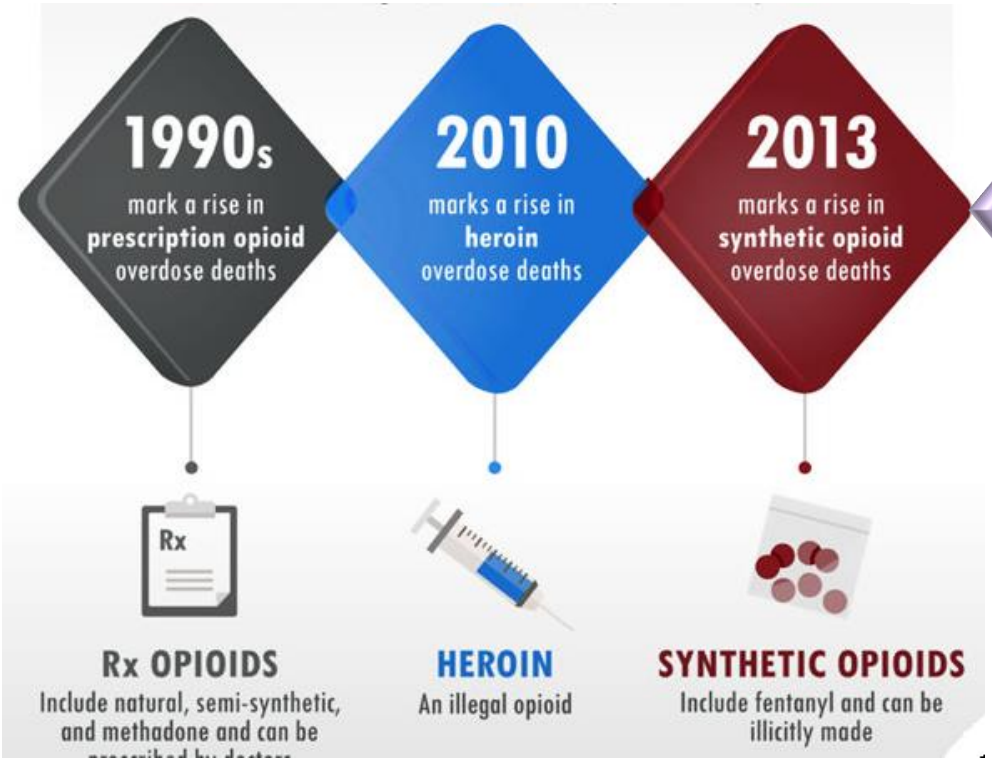


Benzomidazolas (Nitazenos)

- **Opioides sintéticos**

Número y tipo de nuevos opiáceos detectados en la EU (Early Warning System) por primera vez





- Vendidos como substitutos de los opioides tradicionales tambien pueden ser encontrados como adulterantes y en algunos casos son comercializados como medicamentos (e.g oxicodona).

New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

❑ ***Target screening (LCMSMS) vs Unknown compounds (High Resolution Mass Spectrometry – Orbitrap, Tof)***

- Evolución analítica del Laboratorio de Toxicología Forense de Lisboa (INMLCF, IP)

Agilent GC/MS 5973

Waters - UPLC/MSMS TQD

Bruker – GC/LC QToF Impact II
HRMS

2005 | 2007 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2022 | 2025

Waters - LC/MSMS Quattro Micro

Sciex - LC/MSMS QTrap 6500 +

Aquisição de novos equipamentos:
LC-MS/MS Triplo quadrupolo
LC-QToF HRMS

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❑ ***Target screening (LCMSMS) vs Unknown compounds (High Resolution Mass Spectrometry – Orbitrap, Tof)***

2005 | 2007 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2022 | 2025

Waters - UPLC/MSMS *Acquity UPLC / TQ Detector*

Triagem, confirmação e quantificação de drogas de abuso em matrizes biológicas por LC-MSMS

Triagem, confirmação e quantificação de medicamentos em matrizes biológicas por LC-MSMS

GC/MS Agilent 5973

2004

- **Volume de amostra: 0,5 mL**
- **Procedimentos analíticos: 5 (THC; OPI; COC; ANF; MET)**
- **Procedimento de preparação de amostras: SPE**
- **Tempo por análise: 20 min**
- **Substâncias pesquisadas: 20**

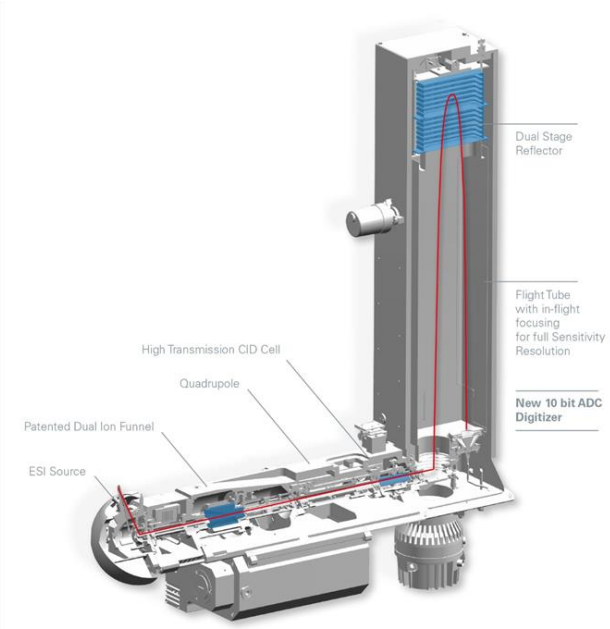
2020

- **Volume de amostra: 0,2 mL**
- **Procedimentos analíticos: 2 (THC; Drogas de abuso)**
- **Procedimento de preparação da amostras: PP**
- **Tempo por análise: 15 min**
- **Substâncias pesquisadas: > 40**

New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

- ***Target screening (LCMSMS) vs Unknown compounds (High Resolution Mass Spectrometry – Orbitrap, Tof)***

Técnica analítica: Liquid Chromatography or Gas Chromatography / High Resolution Mass Spectrometry (QToF)



Bruker – GC/LC QToF Impact II HRMS

- Detetor: Quadrupolo Tempo de Voo (QToF)
- Modos de aquisição principais:
  - **Data Independent Acquisition (DIA) / bbCID**
  - **Data Dependent Acquisition (DDA) / AutoMSMS**

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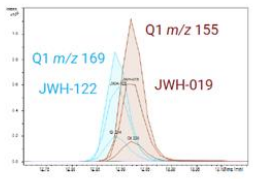
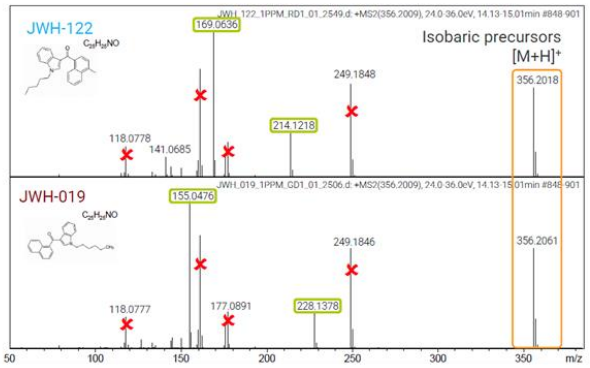
- ***Target screening (LCMSMS) vs Unknown compounds (High Resolution Mass Spectrometry – Orbitrap, Tof)***

2005 | 2007 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | **2022**

Técnica analítica: Liquid Chromatography or Gas Chromatography / High Resolution Mass Spectrometry (QToF)

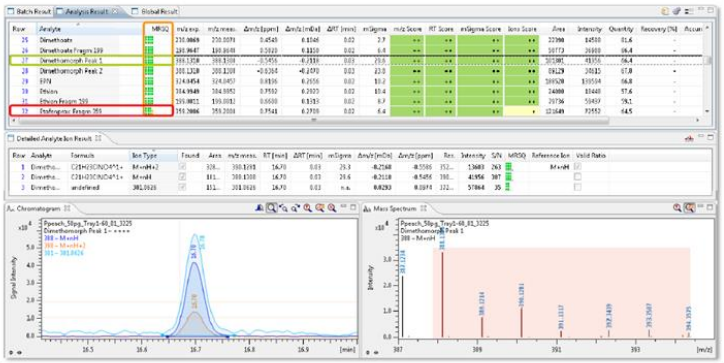
Broad band Collision Induced Dissociation (bbCID)





Bruker – GC/LC QToF Impact II HRMS

Mass accuracy
Retention time (RT)
mSigma (Isotope pattern)
Qualifier (Diagnostic Ions)



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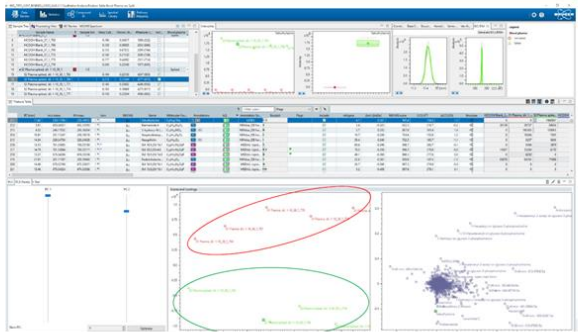
- ***Target screening (LCMSMS) vs Unknown compounds (High Resolution Mass Spectrometry – Orbitrap, Tof)***

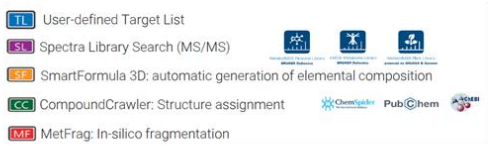
2005 2007 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 **2022** 2025

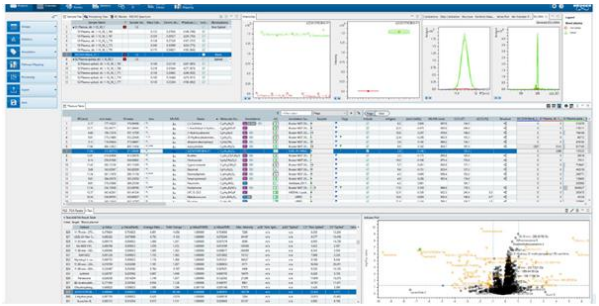
Técnica analítica: Liquid Chromatography or Gas Chromatography / High Resolution Mass Spectrometry (QToF)

Bruker – GC/LC QToF Impact II HRMS

AutoMSMS







New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

❑ ***Target screening (LCMSMS) vs Unknown compounds (High Resolution Mass Spectrometry – Orbitrap, Tof)***

2005 2007 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 **2022** 2025

Técnica analítica: Liquid Chromatography or Gas Chromatography / High Resolution Mass Spectrometry (QToF)

Bruker – GC/LC QToF Impact II HRMS

Vantagens:

- Pesquisa de outras substâncias fora da lista habitual/desconhecidos
- Permite a análise retrospetiva das amostras

Desvantagens / Desafios:

- Elevado investimento económico
- Níveis de sensibilidade inferiores aos triplos quadrupolos topo de gama
- Exige a formação de recursos humanos

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Drogas sintéticas. 60% das novas substâncias detetadas na Madeira e nos Açores

60% dos pedidos de identificação de substâncias feitos ao Laboratório de Polícia Científica da PJ com origem nas ilhas. Consumo de Novas Substâncias Psicoativas tem "peso enorme" em Madeira e Açores.

Novas substâncias psicoativas apreendidas na Madeira quadruplicam em 2022 face a 2021

Em 2017, a PSP confiscou 100 gramas de novas substâncias psicoativas em 2017, num total de oito apreensões, enquanto em 2022 foram apreendidos 12kg e feitas 145 apreensões.

RTP MADEIRA

ESTUDAR COM AUTONOMIA MADEIRA 600 PROG

Expresso 50

SOCIEDADE

Droga nos Açores: substâncias sintéticas muito baratas e abundantes viciam jovens e deixam consumidores "no fundo do poço"

SOCIEDADE

Madeira com «aumento significativo» de internamentos devido a novas substâncias psicoativas

A Casa de Saúde São João de Deus, na Madeira, registou um "aumento significativo" dos internamentos devido ao consumo de novas substâncias psicoativas, disse hoje o diretor da instituição, indicando até junho deste ano já foram assistidas 110 pessoas.

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  - ***Baja incidencia de consumo de NPS en Portugal***
  - ***De entre todos los pedidos de anélisis de NPS realizados al Instituto Nacional de medicina Legal y Ciencias Forenses, 60% son provenientes de las Islas Azores y Madeira***
  - ***Aumento de admisiones en las instituciones de salud debido a episódios psicóticos***
  - ***Precio de venta de las NPS inferior al de las drogas clásicas.***

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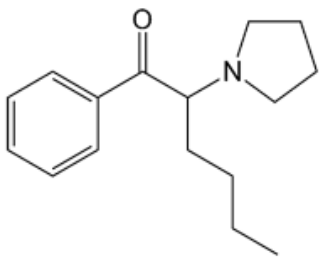
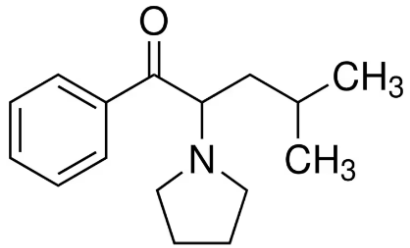


α-PHP (α-Pyrrolidinohexanophenone)



α-PiHP (α-Pyrrolidinoisohexanophenone)

- Synthetic cathinones (pyrovalerone derivatives).
- Street name: “Bloom”.
- Powder or cristal form.
- Strong abuse potential.
- Increase energy and libido, improved mood, empathy and openness in comunication to euforia, hallucinations, anxiety and insomnia.

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Article

OXFORD

Development and Validation of a GC–MS-EI Method to Determine α-PHP in Blood: Application to Samples Collected during Medico-Legal Autopsies

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Region	Sex	Age	Case data	α-PHP concentration in peripherical blood (ng/mL)	Other drugs confirmed
Madeira	Female	56	Undetermined cause of death. Drug addict, with a background of alcoholism, addiction and depression. Cadaver found at home	63	Diazepam, nordiazepam, ethanol
Azores	Male	41	Undetermined cause of death. Drug addict. Consumption of synthetic drugs	227	Diazepam, nordiazepam
Azores	Male	24	Suicide by hanging. Possible consumption of drugs of abuse	160	Alprazolam, diazepam
Madeira	Male	57	Homicide: traumatic injury caused by assault with a knife. Drug addict, medicated with methadone	109	Methadone, EDDP
Madeira	Male	40	Undetermined cause of death. Intestines with purulent contente and signs of necrosis	47	Phenytoin, levomepromazine
Madeira	Male	36	Suspected intoxication with “bloom”. Drug addict with a history of assídous consumption of narcotics	128	Methadone, olanzapine, paracetamol, tramadol, temazepam, oxazepam, nordiazepam, diazepam
Madeira	Male	37	Suicide by jumping off a bridge	60	Morphine, codeine
Azores	Male	31	Traumatic injury from falling from a high place. Regular consumer of synthetic drugs	100	Alprazolam, diazepam, nordiazepam, oxazepam and temazepam.
Madeira	Male	47	Unknown cause of death. Drug addict	215	Methadone, EDDP
Madeira	Male	53	Traumatic injury (domestic accident). Drug addict	195	Diazepam, nordiazepam, ethanol
Madeira	Male	41	Falling from a bridge	30	
Madeira	Male	50	Suicide by hanging. **(α-PiHP)**		Ciamemazine, diazepam, nor-Fluoxetine, olanzapine, paliperidone, risperidone, tramadol

New Psychoactive Substances – Un desafio para los laboratórios de toxicología forense

❑ *Patrones analíticos, cuantos?*

- 7-Aminoclonazepam
- Acetazolamida
- Ácido salicílico
- Ácido valproico
- Aconitina
- α-OH-alprazolam
- Amisulprida
- Amitriptilina
- Amlodipina
- Aripiprazol
- Atorvastatina
- Atropina
- Bisoprolol
- Buflomedil
- Bupropiom
- Buspirona
- Captopril
- Carbamazepina
- Carvedilol
- Norketamina
- Cetoprofeno
- Ciamemazina
- Ciclobenzaprina
- Ciproheptadina
- Citalopram
- Clomipramina
- Clomipramina-D3
- Desmetilclomipramina
- Clonidina
- Cloroquina
- Clorpromazina
- Clozapina
- Desalquilflurazepam
- Desmetilflunitrazepam
- Diclofenac
- Difenidramina
- Digoxina
- Diltiazem
- Donezepilo
- Dotiepina
- Doxilamina
- Duloxetina
- Enalapril
- Ergotamina
- Estricnina
- Etilefrina
- Felbamato
- Fenacetina
- Fenitoina
- Fenobarbital
- Flecaidina
- 7-Aminoflunitrazepam
- Desmetilflunitrazepam
- Fluoxetina
- Norfluoxetina
- Flurazepam
- Fluvoxamina
- Furosamida
- Gabapentina
- Haloperidol
- Harmina
- Hidroclorotiazida
- Hidroxizina
- Ibuprofen
- Imipramina
- Indapamida
- Lacosamida
- Lamotrigina
- Laudonasina
- Lercanidipina
- Levamisole
- Levetiracetam
- Levomepromazina
- Lidocaina
- Lisinopril
- Lovastatina
- Loxapina
- Maprotilina
- Memantina
- Metildigoxina
- Metildopa
- Metoclopramida
- Metoprolol
- Desmetilmianserina
- α-OH-Midazolam
- Mirtazapina
- Desmetilmirtazapina
- Modafinil
- Naloxona
- Naltrexona
- Nifedipina
- Nimesulida
- 7-Aminonitrazepam
- Desmetildotiepina
- Norketamina
- Norpetidina
- Norquetiapina
- Nortriptilina
- Olanzapina
- Oleandrina
- Oxcarbamazepina
- 9-Hidroxirisperidona
- Perindopril
- Propafenona
- Propofol
- Propranolol
- Quetiapina
- Ramipril
- Reboxetina
- Norpetidina
- Piracetan
- Pravastatina
- Pregabalina
- Primidona
- Prometazina
- Propafenona
- Propofol
- Propranolol
- Quetiapina
- Ramipril
- Reboxitina
- Reserpina
- Ricinina
- Risperidona
- Rivastigmina
- Rocuronio
- Selegilina
- Sertralina
- Desmetilsertralina
- Sildenafil
- Sinvastatina
- Solanina
- Sulpirida
- Tadalafil
- Tapentadol
- Temilsartan
- Tetramisol
- Tiagabina
- Tianeptina
- Tiaprida
- Ticlopidina
- Tiopental
- Topiramato
- N-Desmetiltramadol
- O-Desmetiltramadol
- Trazodona
- Triamterene
- Triazolam
- Trimipramina
- Desmetiltrimipramina
- Valsartan
- Vardenafil
- Varfarina
- Venlafaxina
- O-Desmetilvenlafaxina
- Verapamilo
- Vigabatrin
- Vortioxetina
- Ziprasidona
- Zonisamida

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❑ ***Patrones analíticos, cuantos?***

- 11-Nor-9-carboxy-Δ9-THC
- Δ9-THC
- Δ9-THC-D3
- (S) –Anfetamina
- 11-hydroxy-D9-THC
- 11-hydroxy-D9-THC-D3
- 6-Acetilmorfina
- 6-Acetilmorfina-D3
- Alprazolam
- α-PHP
- α-PHP-D8
- α-PHiP
- Benzoilecgonina
- Benzoilecgonina-D3
- Bromazepam
- Buprenorfina
- Busulfan
- Canabidiol
- Canabidiol-D3
- Canabinol
- Canabinol-D3
- Clordiazepóxido
- Clobazan
- Clonazepam
- Cocaetileno
- Cocaetileno-D3
- Cocaina
- Cocaina-D3
- Codeina
- Codeina-D3
- Diazepam
- Diazepam-D5
- Ecgonina metil ester
- EDDP
- Estazolam
- Etilfenidato
- Fentanil
- Fentanil-D5
- Norfentanil
- Flunitrazepam
- Flurazepam
- GBL
- GHB
- HMMA
- Hidrocodone
- Hidromorfona
- Isotonitazeno
- Isotonitazeno-D7
- Ketamina
- Loprazolam
- Lorazepam
- Lormetazepam
- Losartan
- LSD
- M-CPP
- Medazepam
- Mefedrona
- Mefedrona-D3
- Metcatinona
- Metilfendato
- Metonitazeno
- Midazolam
- Morfina
- Morfina-D3
- Nitrazepam
- Nordiazepam
- Oxazepam
- Oxicodona
- Pentobarbital
- Pentobarbital-D5
- Petidina
- Prazepam
- Psilocina
- Rac-Anfetamina
- Rac-Anfetamina-D6
- MBDB
- MDA
- MDA-D5
- MDEA
- MDEA-D5
- MDMA
- MDMA-D5
- Metadona
- Metadona-D3
- Metanfetamina
- Metanfetamina-D9
- Sufentanil
- Temazepam
- Tramadol
- Trans-11-nor-9-carboxy-D9-THC-D3
- Triazolam
- Zolpiden