Monitoring and responding to new psychoactive substances in Europe

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3-step approach


I. Information exchange
   Early-warning system (EWS) → EMCDDA-Europol Joint Reports

II. Risk assessment → EMCDDA Risk Assessments

III. Decision-making → Council Decisions on control
2014 overview

- 101 new substances notified (37 in 2015)
- 16 public health alerts
- 6 risk assessments (25I-NBOMe, AH-7921, methoxetamine, MDPV, 4,4'-DMAR, MT-45)
- New opioids (MT-45, 28 deaths)
- Stimulants (4,4'-DMAR, 30+ deaths)
- Dissociative anesthetics (diphenidline, 2-MeO-diphenidline)
- Dietary supplements aimed at broader population
2014 overview

- **SCRAs** (5F-PB-22, MDMB (N) BZ-F). Recent outbreaks in Russia, United States

  2015 Outbreaks of 'Spice' intoxications in the US - 3,387 exposures reported to US poison control centres Jan 1 to May 20. - 72% reported between 1 April to 20 May — outbreaks reported in some States linked to ADB-CHMINACA - e.g Mississippi: Since April 2, 2015, there have been 1,191 reports of spice-related visits to emergency rooms, hospitals, or physicians in Mississippi. Sixteen deaths potentially related to spice use are being investigated. [https://twitter.com/toxicovigilance/status/596724034936635392](https://twitter.com/toxicovigilance/status/596724034936635392)

- **Medicines** (either diverted or sold as illicit drugs)

- **Production within EU**, involving OCGs

- **Strengthen toxicovigilance** (identification, reporting, understanding serious adverse events)

  - **Public health alerts** (first signal, further cases)

    - greater use of **OSINT**
The EWS — triangulation of multi-source information

Multidisciplinary partners
- Forensic science and toxicology networks
- Health and care system
- Law enforcement agencies
- Relevant national agencies
- ‘Street’ level key informants
- Other

Open source information
Internet, media, users, scientific/grey literature

Targeted research
test purchase, wastewater analysis, computational modelling, pharmacotoxicological profiling

the EWS information sources

Reporting
forensic analysis
toxicology, law enforcement, surveys, health & care

the EWS Network
Poison centres
Multisector regulation
Int. partners
Researchers
Customs
Treated service promotion
Reitox
Forensic scientists
Health
Academics
Clinical toxicologists
Emergency clinicians
Policy makers
Forensic toxicologists
Police
NGOs
Number of new psychoactive substances reported to the EU Early Warning System, 2005–14

101 in 2014
450+ monitored
50% appeared in last 3 years
Close to double the number of substances controlled under the UN Conventions
Number of NPS monitored by the EWS by category

450+ substances monitored

- Synthetic cannabinoids
- Phenethylamines
- Opioids
- Arylamines
- Synthetic cathinones
- Benzodiazepines
- Others
- Tryptamines
- Piperazines

Substances examples:
- 25I-NBOMe
- 4,4'-DMAR
- MDPV
**Legal highs**
Marketed in bright and attractive packaging. Sold openly in head/smart shops and online. Aimed at recreational users.

**Research chemicals**
Sold under the guise of being used for scientific research. Aimed at 'psychonauts' who explore the effects of psychoactive substances. Sold openly online.

**Food supplements**
Sold under the guise of being food or dietary supplements. Aimed at people wanting to enhance their body and mind. Sold openly in fitness shops and online.

**Designer drugs**
Passed off as drugs such as MDMA and heroin. Produced in clandestine labs by organised crime. Sold on illicit drug market by drug dealers.

**Medicines**
Medicines that are diverted from patients or illegally imported into Europe. Sold on illicit drug market by drug dealers.
NPS
not under UN Conventions

- failed medicines
  - MT-45
- pharmacological probes
  - 25I-NBOMe
- withdrawn medicines
  - DMAA
- novel substances
  - methoxetamine 4,4’-DMAR
- investigational medicines
  - CRA13
- APIs (medicines)
  - pregabalin, phenibut
- accident
  - 4-MA
  - 4-FA
From synthesis to consumer

1. Chemical companies based in China and India synthesise NPS in bulk quantity.

2. Shipped by air or sea to Europe.

3. Processed and packaged into legal highs, research chemicals and food supplements.

4. Sold openly in head/smart shops and online.

5. 8% lifetime use in young adults.
Seizures in 2013

46730 seizures
3.1+ tonnes
Cannabinoids and Cathinones:
~70% of seizures
~85% of weight
Number of seizures of new psychoactive substances and quantity seized, 2005–13

Note: 2009 data exclude six tonnes of ketamine seized by one country, due to a lack of contextual information.
Cannabinoids

New in 2014: 30
Currently monitoring: 134

In 2013:
21495 seizures
1.6 tonnes

- 0.6 tonnes of powder, often in bulk amounts
- 10 cannabinoids accounted for approximately 90 % of the total weight of powders
Number of synthetic cannabinoid seizures and quantity seized, 2008–13

200-fold increase in seizures 2008–13
Rapid replacement of synthetic cannabinoids on the European market

<table>
<thead>
<tr>
<th>Substance</th>
<th>JWH-018</th>
<th>JWH-018 adamantyl derivative</th>
<th>JWH-018 adamantyl carboxamide (Apica)</th>
<th>AKB48 (Apinaca)</th>
<th>5F-AKB48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of first detection</td>
<td>2008</td>
<td>2011</td>
<td>2012</td>
<td>2012</td>
<td>2012</td>
</tr>
<tr>
<td>Number of seizures in 2013</td>
<td>162</td>
<td>8</td>
<td>98</td>
<td>404</td>
<td>3 362</td>
</tr>
</tbody>
</table>
e-liquids containing synthetic cannabinoids

An emerging market

May contain a mix of different synthetic cannabinoids

Great potential for overdose

May contain nicotine

‘Dutch Apple’ contains 5F-AKB48
Cathinones

New in 2014: 31
Currently monitoring: 77
In 2013:
10657 seizures
1.1+ tonnes
- 341kg 3-MMC
- 201kg 4-MEC
- 197kg pentedrone
Number of synthetic cathinone seizures and quantity seized (powders), 2005–13

60-fold increase in seizures 2008–13
Toxicovigilance (ToV) is the active process of detecting, reporting, evaluating, understanding, monitoring and responding to adverse events associated with new psychoactive substances.

In the context of early warning it focuses on **serious adverse events** - information which allows us to identify an emerging toxicological problem — both acute and chronic — allowing earlier response at national and EU-level.

Adapted from WHO.
Toxicovigilance and early warning
Public health alerts

117 public health alerts issued since 2005

70%+ issued in the last five years.

16 alerts were issued in 2014

2 examples from 2015 are presented below
1 serious non-fatal intoxication associated with butyrfentanyl (N-[1-(2-phenylethyl)-4-piperidyl]-N-phenylbutyramide).

The Swedish National Focal Point has reported 1 serious non-fatal intoxication associated with butyrfentanyl. The case involved a male aged in his mid-twenties and occurred in May 2014. As far as we know this is the first such case to be reported to the Early Warning System.


The data was provided by the Swedish Poisons Information Centre.

**Overview of detections in Europe**

Butyrfentanyl was first notified in September 2014. This was based on its identification in three seizures made in July 2013 in Poland that were linked to organised crime groups involved in the production, trafficking and use of the substance. The seizures comprised: 1) 5g of a white/yellow powder; 2) 200g of white powder in a 1:100 mixture with lactose; and, 3) 290g of white powder in a 1:100 mixture with lactose. In addition, authorities in Sweden identified the substance in a seizure of 9.59g of pale yellow powder made in April 2014.

**Chemical and analytical details**

Butyrfentanyl is the butyryl homologue of the opioid analgesic fentanyl [1,2]. The synthesis of butyrfentanyl was first described by Janssen in 1961 [1,2]. Analytical characterisation has been reported by Ohta et al., Suzuki, and, Brine et al., [1,3–5].

Other names and abbreviations: N-(1-phenethyl)-4-piperidyl)butyranilide; n-propylfentanyl; butyryl fentanyl; NIH 10486; B-F; fentanyl butanamide analogue.

**Pharmacology* and toxicology**

Data on the analgesic activity of a series of fentanyl analogues indicate that 'butyryl fentanyl' is about twelve times less active than fentanyl in the rat [1,6]. In a recent study using the writhing-method in mice, Higashikawa and Suzuki [1,7] compared the oral analgesic activity of a series of opioids and the following potency order (relative to morphine) was established: α-methylfentanyl (56.9) ≈ fentanyl (54.1) > 'butyryl fentanyl' (7.0) ≈ 'isobutyryl fentanyl' (6.9) > morphine (1). In a rat brain opioid receptor binding assay the EC50 values for morphine and the butyryl and isobutyryl homologues of fentanyl were 24, 59 and 85 nM, respectively; both homologues functioned as receptor agonists [8]. In study with a rat brain receptor preparation using tritiated fentanyl as the radioligand, the affinity Ki values for fentanyl, α-methylfentanyl, 'butyryl fentanyl' and the N-benzyl analogue of fentanyl were 1.1, 1.6, 32, and 210 nM, respectively [1,9]. Data from single-dose suppression (SDS) studies conducted by Aceto et al., in Rhesus monkeys found that butyrfentanyl (called 'NIH 10486') substituted completely for morphine. The drug had a quick onset of action. Duration of action was at least 2 1/2 hr. At peak effect, the drug was 10-20X more potent than the reference standard morphine. At the highest dose, the signs jaw sag, ataxia, slowing, scratching and severe body sag were noted [10]. Further data on the pharmacology of butyrfentanyl are available in the references listed below.

Data are not available on the toxicology of butyrfentanyl.

**Epidemiology**

Information on the use of butyrfentanyl is largely limited to self-reported experiences on user websites, see: https://www.google.pt/search?q=butyrfentanyl

**EDND profile**

Further information on butyrfentanyl can be found on the EDND at: https://ednd.emcdda.europa.eu/html.cfm/index7246EN.html?SUB_ID=434&detail
Please note

As with all alerts transmitted by the EWS please remember that they may contain information that could be regarded as sensitive. Should you provide some of the information 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 do contact us.

We would be grateful if you could forward any further information that you have on butyrfentanyl to: ews@emcdda.europa.eu

References


*Note this section has been abstracted from Ujváry [1].
9 non-fatal intoxications associated with diphenidine (1-(1,2-diphenylethyl)piperidine).

The Swedish National Focal Point have reported 9 analytically confirmed non-fatal intoxications associated with diphenidine that occurred between February and May 2014. Analysis was limited to urine. 8 of the patients were male and 1 was female; they were aged between 19 and 46 (mean 32). In addition, the report notes a further 9 non-fatal intoxications which were not analytically confirmed; in most of these cases there were other substances involved. As far as we know these intoxications represent the first cases associated with diphenidine that have been reported to the Early Warning System.

The available information from the 9 analytically confirmed cases are presented below:


Case 5. Substances detected: diphenidine; 3-MeO-PCP; butylone; 5-APB/6-APB; buprenorphine; oxazepam; temazepam; metabolites of ethanol.


Case 7. Substances detected: diphenidine.


In summary, symptoms were reported for 5 of the 9 analytically confirmed cases. These were: tachycardia (n=3 cases), somnolence (n=2), mydriasis (2), confusion/disorientation (2), hypertension (2), dry skin and mouth (1), cold sweating (1), pale (1), anxiety (1). Note that in 3 cases (case 1, 3 and 8) other substances were detected along with diphenidine which may have played a role in the intoxication and hence reported symptoms.

The data was provided by the Swedish Poisons Information Centre.

**Background on diphenidine**

Diphenidine was first notified by the United Kingdom and Italy in January 2014. In the case of the United Kingdom the notification was based on its identification in a collected sample purchased from an Internet retailer. In the case of Italy, the notification was based on a seizure made of a package in the incoming mail. Subsequently, it has been detected in 5 other countries (DK, FI, HU, NO, SE). A history of diphenidine which focuses on its emergence on the drug market is provided by Morris and Wallach [1].

**Chemical and analytical details:**

Diphenidine is an diarylethylamine. It can be regarded as a MK-801 (dizocilpine) homeomorph and shares structural features with arylcyclohexylamines [1]. The synthesis of diphenidine was first described by Christiaen in 1924 [1]. The contemporary preparation and analysis of diphenidine are provided in Wallach et al., [2]. Analytical data has also been provided by Rossi et al., [3].
Pharmacology:

Data from *in vitro* studies has demonstrated that racemic, but also *(S)*- and *(R)*-diphenidine bind to NMDA receptors, with diphenidine acting as an antagonist [1,2]. A recent study by Wallach et al., using rat hippocampal slices confirmed this, finding that the substance reduces NMDA-mediated field excitatory postsynaptic potentials similar, albeit slower, to ketamine [2]. Metabolites of diphenidine were not studied.

Self-reported user experiences suggest that diphenidine is a dissociative anaesthetic type drug. Morris and Wallach note that users have reported ‘mild effects at doses of 50–100 mg, with strong dissociative effects starting at oral doses of 110 mg and higher doses inducing bizarre somatosensory phenomena and transient anterograde amnesia, lasting 3–6 h’ [1]. They also note that diphenidine shows variability in qualitative effects and duration, with higher doses having residual psychoactive effects that can last several days. Users also report a steep dose response curve. Importantly some users have begun to report troubling responses including tachycardia, hyperthermia, and hospitalisation due to seizures with higher doses of diphenidine and/or 2-MeO-diphenidine’ [1].

Further details on self-reported experiences are available on user websites:

http://www.bluelight.org/vb/threads/668291-The-Big-amp-Dandy-Diphenidine-Thread

Other reports of serious adverse events:

A review of open source information did not identify any published serious adverse events associated with diphenidine.

Adverse events have been reported on user websites; see links to user websites provided above.

Other relevant information:

Japanese authorities have reported the detection of both diphenidine (289 mg/g) and the synthetic cannabinoid 5F-AB-PINACA (55 mg/g) in a ‘legal high’ type product called ‘ALADDIN SPACIAL EDITION’ which appeared to be a herbal smoking mixture [4].

EDND profile:

Further information on diphenidine can be found on the EDND at https://ednd.emcdda.europa.eu/html.cfm/index7246EN.html?SUB_ID=379&detail

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References

EMCDDA risk assessment of NPS


- 4-MTA
- PMMA
- 2C-I
- 2C-T-2
- 2C-T-7
- TMA-2
- Mephedrone
- 5-IT
- MBDB
- Ketamine
- GHB
- BZP
- 4-MA
- MDPV
- Methoxetamine
- 25I-NBOMe
- AH-7921
- 4,4’-DMAR
- MT-45

> 30 ‘new synthetic drugs’ notified
9 risk assessments
6 substances controlled

~ 490 new psychoactive substances notified
10 risk assessments
8 substances controlled

Joint Action 97/396/JHA
Council Decision 2005/387/JHA
4,4’-DMAR timeline

- **Formal notification to EWS**: 10/12/2012
- **EWS alert**: 8 deaths in Hungary, 03/10/2013
- **Joint Report**: Procedure launched, 28/02/2014
- **Joint Report submitted to the EU institutions**: 08/05/2014
- **Risk Assessment**: 16/09/2014

- **19/11/2012**: Netherlands customs seizure 500 g powder
- **06/02/2014**: EWS alert, 18 deaths in UK
- **27 deaths**
- **31 deaths**
- **1 NFI**
MT-45 timeline

- **Formal notification to EWS**
  - 05/11/2013

- **EWS alert**
  - 11 deaths and 2 NFIs in Sweden
  - 25/02/2014

- **Joint Report procedure launched**
  - 16/04/2014

- **Joint Report submitted to the EU institutions**
  - 25/06/2014

- **Risk Assessment**
  - 16/09/2014

- **15/10/2013**
  - Sweden customs seizure 50g powder

- **05/03/2014**
  - Belgium collected sample of powder
  - MT-45+ methylone

- **21 deaths**
  - 13 NFIs

- **28 deaths**
  - 18 NFIs
Changes in national legal responses since 2009

**New NPS laws**
- Catch-all
- Lists or group definitions.

**Modifying drug laws**
- Risk assessment
- Group definitions
- Temporary controls

**Existing non-drug (other) laws**
- Consumer health/safety
- Medicinal products

Supply
- Use or supply
- Supply
Recent years have witnessed a proliferation of new psychoactive substances becoming available in Europe. The phenomenon has provoked a range of innovative legal responses geared towards controlling the open sale of these substances. The map shows innovations from around Europe.

Click on a marker on the map to learn about it. Each one is colour-coded, depending on the type of innovation. Numbers are assigned chronologically (i.e., smaller numbers are for earlier innovations).
Thank you

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