New Psychoactive Substances in Europe - An update on diversity and trends from the EU Early Warning System

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Regional Workshop on New Psychoactive Substances (NPS) for South Eastern Europe
What is a new psychoactive substance?

Council Decision 2005/387/JHA defines a new psychoactive substance as a:

‘New narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the 1961 or the 1971 UN Conventions, but which may pose a public health threat comparable to that posed by substances listed in Schedule I or II or IV of the former and in Schedule I or II or III or IV of the latter convention’.
Definitions

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.
The EU Early Warning System


I. Information exchange
Early warning system (EWS)

II. Risk assessment

EMCDDA–Europol Joint Reports

EMCDDA Risk assessments
(http://www.emcdda.europa.eu/publications/searchresults?action=list&type=PUBLICATIONS&SERIES_PUB=w12)

III. Decision-making

Council Decisions on control
since 1997

EMCDDA
Early Warning System

signal identification
early warning
rapid response
risk assessment

EMA
pharmacovigilance

30
REITOX national early warning systems

Europol
organised crime

COM

data collection
data management
capacity building
analysis

police medicine regulators
public health treatment providers
chemists pathologists researchers

toxicologists policy makers poison centres researchers

since 1997
What is the scope of the EU EWS?

- **New psychoactive substances** - ‘New’ to the drug market or newly misused

- **Changes in purity** of established (controlled) drugs

- **Established (controlled) drugs adulterated with unusual and/or harmful cutting agents** e.g. Anthrax outbreak among heroin injecting drug users, cocaine adulterated with levamisole, etc.

- **Substances sold as others** e.g. Heroin sold as cocaine

- **New patterns (forms) of use** e.g. Injection of cathinones

- **Fatal and non-fatal intoxications**

- **Large seizures**, seizures that show evidence of international trafficking and/or involvement of organised crime
Reporting forms

3. Source of information (fill one or more as appropriate)

Seizure(s) □ Specify amount (weight, number, of tablets, etc.):

Seizing authority:
Date: Place:

Biological sample(s) (1) □ Specify type:
Identifying authority:
Date: Place:

Collected sample(s) (2) □ Specify amount (weight, number, of tablets, etc.):
Collecting authority:
Date: Place:

Other substances present (if more than one case, specify for which one):
Psychoactive ingredients:
Other ingredients:

(1) Biological (human) samples e.g. body fluids (urine, blood), tissues, hair, etc.
(2) Actively collected by drug monitoring systems for monitoring or research purposes
The EWS – triangulation of multi-source information

Multidisciplinary partners

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

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

Reporting
forensic analysis,
toxicology,
law enforcement,
From synthesis to consumer...

Chemical companies in China and India synthesise the NPS powder in bulk.

The NPS powders are shipped to Europe by air and sea.

8% young Europeans has used NPS in their life (Eurobarometer, 2014)

Legal highs, research chemicals and dietary supplements are processed and packaged in EU.

They are sold openly in shops and on the Internet.
Number of NPS reported to the EWS (2005-2014)

101 NPS reported for the first time in 2014

>450 NPS currently monitored

all detections analytically confirmed
Seizures of NPS in 2013

47,000 seizures amounting to more than 3.1 tonnes in Europe

299 different NPS detected in 2013

Cannabinoids and cathinones make up:

~70% of seizures
~85% of weight
Number and quantity of NPS seizures 2005-2013

Number of seizures of new psychoactive substances and quantity seized, 2005–13

7-fold increase in seizures 2008–13

Note: 2009 data exclude six tonnes of ketamine seized by one country, due to a lack of contextual information.
Number and quantity of synthetic cannabinoid seizures 2008-2013

21,495 seizures amounting to almost 1.6 tonnes in 2013

182 kg AM-2201, 115 kg 5FUR-144 and 114 kg 5F-AKB48 powder seized in 2013
Categories of cannabinoids seized from 2008-2013
Number and quantity of synthetic cathinone seizures 2005-2013

10,657 seizures amounting to more than 1.1 tonnes in 2013

77 synthetic cathinones monitored by the EWS

- 341 kg 3-MMC
- 201 kg 4-MEC
- 197 kg Pentedrone
‘Significant’ cathinones

- Methylone
- Mephedrone
- MDPV
- Pentedrone
- 4-MEC
- α-PVP

[Graph showing the number of seizures for each cathinone from 2005 to 2013]
Toxicovigilance

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.
Serious adverse event means any adverse event associated with the consumption of a new psychoactive substance in a human that:

- results in **death**;

- is **life-threatening**;

- requires **hospitalisation**;

- results in **persistent or significant disability or incapacity**;

- consists of a **congenital anomaly or birth defect**;

- or is **an important medical event** that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also be considered serious.

-Examples of such events are **intensive treatment in an emergency room**; convulsions that do not result in hospitalisation; or **development of substance**
Toxicovigilance and early warning
4. Risk Assessment
Number of NPS monitored by the EWS by category

- 450+ substances monitored
- 6 risk assessments
- 16 public health alerts in 2014
- 6 substances associated with >200 deaths and >700 non-fatal
Risk assessment of NPS

*Critically reviewed at 36th ECDD meeting

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

> 30 ‘new synthetic drugs’ notified
9 risk assessments
6 substances controlled
Under the terms of the Joint Action 97/396/JHA

~ 490 new psychoactive substances notified
10 risk assessments
8 substances controlled
Under the terms of the Council Decision 2005/387/JHA
## Risk assessment

| A) Physical, chemical, pharmaceutical and pharmacological information |
| B) Dependence and abuse potential |
| D) Health risks |
| E) Social risks |
| F) Involvement of organised crime |
| C) Prevalence level |

Semi-quantitative assessment procedure – risks relative to other substances
Case study: MT-45

- **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**
4. New concerns and challenges
New concern: injection of synthetic cathinones

Mephedrone, MPDV, pentedrone, 4-MEC and alpha-PVP (aka flakka) have carved a space in the illicit stimulants market in some countries.

Prevalence levels remain low but injection a concern

Widespread IDU: HU, RO
Pockets of IDU: AT, ES, FR, IE, UK

EWS alert issued on cathinone 4F-α-PVP on 23 October 2014

[EWS Alert]: 2 deaths associated with 4F-α-PVP (1-(4-fluorophenyl)-2-((2-methyl-1,3-dioxolane-4-y) methyl)piperazine) in Sweden
New concern: highly potent synthetic opioids

Being used as substitutes for heroin/morphine

Indicates a change in the types of users attracted to NPS

Examples: AH-7921, carfentanil, ocfentanil, W-15

Some are extremely potent (fentanyls)

HOW MUCH PURE DRUG IS NEEDED TO MAKE 10 000 DOSES?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amount Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfentanil</td>
<td>0.1 g</td>
</tr>
<tr>
<td>3-Methylfentanyl</td>
<td>2.5 g</td>
</tr>
<tr>
<td>25I-NBOMe</td>
<td>5 g</td>
</tr>
<tr>
<td>PB-22</td>
<td>100 g</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>100 g</td>
</tr>
<tr>
<td>Cocaine</td>
<td>200 g</td>
</tr>
<tr>
<td>MDMA</td>
<td>750 g</td>
</tr>
</tbody>
</table>

- New drugs
- 'Old' drugs
Fentanyl is a potent opioid analgesic of the phenylpiperidine class and is structurally similar to fentanyl. It is also known as desmethyl fentanyl and is considered to be five times more potent than heroin.* Has been seized in 4 Member States since 2014. In some of these seizures a known precursor in fentanyl production (4-ANPP/ANPP) was also detected.

The United States Drug Enforcement Agency (US DEA) is aware of at least 25 confirmed fatalities involving acetyl fentanyl between 2013 and 2014.
Replacement of synthetic cannabinoids on the NPS market

<table>
<thead>
<tr>
<th>Substance</th>
<th>JWH-018</th>
<th>JWH-018 adamantyl derivative</th>
<th>JWH 018 adamantyl carboxamide</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>3362</td>
</tr>
</tbody>
</table>
Synthetic cannabinoid receptor agonists
Classification by mode of action

http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids

Naming system currently used by the EMCDDA for newly detected synthetic cannabinoids:

Ring-TailCoreLinker

Example: MDMB-CHMICA

The **Ring** element would be MDMB (methyl dimethyl butanoate)
The **Tail** element would be CHM (cyclohexylmethyl)
The Core element is I (indole)
And the **Linker** element is CA (carboxamide)

Example: ADB-CHMINACA

The **Ring** element would be ADB (amino dimethyl butanone)
The **Tail** element would be CHM (cyclohexylmethyl)
The Core element is INA (indazole)
Naming of Synthetic Cannabinoids

If the substance were to have a core substituent for example 5-fluoropentyl then we would place this at the start of the name i.e. 5F-Ring-TailCoreLinker.

Some of the codes that we are using in this system:

I = indole
INA = indazole
CA = carboxamide
FUB = 4-fluorobenzyl
NA = napthyl
CH = cyclohexyl
CHM = cyclohexylmethyl
Py = pyrrole
P = pentyl
Identification of NPS – challenges

- Lack of reference standards
- Identification of isomers
- Increasing numbers of mixtures
- Difficulties in identification (don’t know what your looking for)
- Limited forensic capacity and available expertise of analytical laboratories (NMR)
- Lack of formal pharmacokinetic and pharmacodynamic studies – unknown metabolites
- Selectivity and sensitivity of screening tests
Identification of NPS in biological samples

- Identification of isomers (e.g. positional isomers)
- Mixtures of substances (in different amounts)
- Lack of formal pharmacokinetic and pharmacodynamic studies – unknown metabolites
- Selectivity and sensitivity of screening tests:
  low doses → low blood concentrations
- Rapid metabolism → parent substance can only be detected for a short period of time
Wastewater analysis
Wastewater analysis

Detection of designer drugs in waste water
A pilot study in Helsinki area, Finland

Wastewater analysis / sewage epidemiology

Sources of uncertainty

Sources of variability

http://www.emcdda.europa.eu/wastewater-analysis
“It is likely that the future drugs of abuse will be synthetics rather than plant products. They will be synthesised from readily available chemicals, may be derivatives of pharmaceuticals, will be very potent, and often very selective in their action. In addition, they will be marketed very cleverly.”

- Henderson, 1988
Thank you for your attention


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