The EU Early Warning System on new psychoactive substances
How to spread analytical knowledge in laboratories

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WADA Science and Investigations Symposium, Istanbul, 28 October 2014
EMCDDA: the EU drug information agency
28 Member States, Turkey and Norway

• A decentralised agency of the European Union based in Lisbon. Provides the EU and its Member States with a factual overview of European drug problems and a solid evidence base to support the drugs debate

• Under a three-step legal framework, EMCDDA plays a central role in identifying, monitoring and responding to new drugs

• Implements the real time EU Early Warning System on new drugs with national early warning systems from 30 European reporting countries, Europol, European Medicines Agency, European Commission, since 1997

• Forensic science at the core of the system

• Carries out the EU risk assessment of new drugs through its Scientific Committee
Council Decision 2005/387/JHA
EMCDDA – Europol annual implementation reports

I. Information exchange
Early warning system (EWS)

II. Risk assessment

III. Decision-making

More than 15 years of regional monitoring
(30 reporting countries)

Joint Report
Biannual EWS reports
Reporting forms (ad hoc)

European Database on New Drugs (EDND)
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’.
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

### Reporting
- Forensic analysis, toxicology, law enforcement, surveys, health & care

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**the EWS information sources**
Drugs 2.0
The new drug phenomenon in the EU today

Five broad and overlapping groups. Most are synthetic substances

- **‘Legal highs’**: sold openly, often as branded products in sophisticated packaging. Sold on the Internet, in head shops and by street-level drug dealers. Also called bath salts, plant food, incense

- **‘Research chemicals’**: largely sold online as zip-locked bags of powder with labelled chemical content

- **Medicines**: diverted within EU (pregabalin, benzydamine, gabapentin) or imported (phenazepam, phenibut)

- **Dietary supplements**: aimed at lifestyle users, sold on in bricks and mortar shops and online (e.g. eBay). Phenibut, DMAA

- **‘Designer drugs’**: sold on illicit market as ‘ecstasy’ (mCPP, PMAA) or ‘speed’ (4-methylamphetamine) or heroin (fentanyl). Users mostly unaware that they are taking them
Where do NPS come from?

- ‘Failed’ medicines (AH-7921)
- Withdrawn medicines (DMAA)
- Investigational medicines (CRA13)
- APIs used in medicines authorised outside EU (phenibut)
- APIs used in medicines authorised in EU (fentanyl, pregabalin)
- Pharmacological probes (25I-NBOMe)
- Novel substances (methoxetamine)
AH-7921 (3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide)

‘Failed’ medicine, sold as a ‘research chemical’ (EU)

Invented and patented by Allen & Hanburys Limited in the mid-1970s. Analgesic properties studied in non-clinical trials in the 1970s. Development into a medicine was abandoned for unknown reason. Since 1989, no studies have been published. Suddenly in 2010, Internet chatter (open source information) begins on AH-7921.
Increasingly diverse drug groups

- Arylalkylamines
- Aminoindanes
- Medicines. & derivatives
- Synthetic.cocaine.substitutes
- Phenethylamines
- Piperazines
- Synthetic.Cannabinoids
- Cathinones
- Tryptamines
- Others
- Narcotic.analgesics
- Plants. & Extracts
- Piperidines. & pyrrolidines
- Aminocyclohexanes
Reclassification of drug families
### Reclassification of drug families – based on chemistry

<table>
<thead>
<tr>
<th>Family</th>
<th>Chemical substructure</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Arylcyclohexylamines</td>
<td></td>
<td>ketamine, tramadol, phencyclidine/PCP, methoxetamine</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aminoindanes</td>
<td></td>
<td>1-aminoindane, 2-aminoindane, MDAI</td>
</tr>
<tr>
<td>Arylalkylamines</td>
<td></td>
<td>bromo-dragonfly, thienoamphetamine, 6-APB</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td>Diazepam, Phenazepam, Flubromazepam, Pyrazolam</td>
</tr>
<tr>
<td>Piperidines &amp; pyrrolidines</td>
<td></td>
<td>ethylphenidate, desoxypropadrol/2-DPMP, diphenylprolinol/D2PM</td>
</tr>
</tbody>
</table>
Increase of the number and diversity of new drugs

- Opioids
- Benzodiazepines
- Arylalkylamines
- Piperidines & pyrrolidines
- Plants & extracts
- Aminoindanes
- Arylcyclohexylamines
- Synthetic cannabinoids
- Cathinones
- Piperazines
- Tryptamines
- Phenethylamines
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

Little evidence available
Risk assessment of NPS

* Critically reviewed at 36th ECDD meeting


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5-(2-aminopropyl)indole (5-IT)

Sold as a 'research chemical' and found in 'legal high' product

5-(2-Aminopropyl)indole (5-IT) is a substituted indole and a positional isomer of the tryptamine alpha-methyltryptamine (AMT)

First notified through the EWS by the Norwegian FP in June 2012
Their differentiation can be a challenge under routine analytical conditions, especially when reference material is unavailable
In *July 2012*, deaths related to an unknown substance were notified by the EWS – in one case, MS matched AMT but a plastic bag labelled ‘5-IT’ was found on the scene. The Swedish National Board of Forensic Medicine obtained a reference standard, developed and validated TOF screening for 5-IT and re-evaluated retrospectively all autopsies from April onwards in a short period of time. 24 deaths were linked to 5-IT in five months – the EMCDDA launched the risk assessment on 5-IT in October 2012.
Analysis of ‘legal high’ products

Challenges

- similar chemical, chromatographic and spectral properties
- not included in commercially available spectra libraries
- lack (or limited) reference standards
Synthetic cannabinoid receptor agonists

- Naphthoylindoles (JWH-018)
- Phenylacetylindoles (JWH-250)
- Cyclohexylphenols (CP47,497)
- Tricyclic terpenoid (HU-210)
- Benzoylindoles (RCS-4)
- Naphthoylpyrroles (JWH-307)
- Naphthoylnaphthalenes (CRA-13)
- Adamantylindoles (JWH-018 deriv.)
- Allosteric modulators (Org27569)
- Quinones (HU-331)
- Cyclopropylindoles (UR-144)
- Benzoazinones (URB754)
- Indazole (APINACA)

- Chemically diverse, grouped by mode of action
- 130 monitored by the EWS
Mass spectra of positional isomers of mephedrone
virtually identical fragmentation

All have the same molecular formula: C$_{11}$H$_{15}$NO & exact mass: 177

BUT:
only the 4-methyl isomer (4-MMC, mephedrone) is controlled throughout EU
IR spectra of positional isomers of mephedrone

similar but NOT identical
Positional isomers of mephedrone: separation of by HPLC

All have the same molecular formula: $C_{11}H_{15}NO$

**BUT:**
only the 4-methyl (4-MMC) isomer is controlled
$^1$H NMR spectra of positional isomers of mephedrone clearly different

protons of the aromatic region only are shown (at 600 MHz; in CDCl$_3$)
Forensic identification key to enforce control measures

3-Methylmethcathinone is not controlled – Identification of positional isomers !!!

Diário da República, 1.ª série—N.º 61—26 de março de 2012
Artigo 2.º

Alteração das tabelas anexas ao Decreto-Lei n.º 15/93, de 22 de janeiro

São aditadas à tabela I-A e à tabela II-A, anexas ao Decreto-Lei n.º 15/93, de 22 de janeiro, respetivamente, a substância tapentadol (3-[(1R,2R)-3-(dimetilamino)-1-etil-2-metilpropil]fenol) e a substância 4-metilmethcathinona (mefedrona).

Diário da República, 1.ª série—N.º 75—17 de abril de 2013

ANEXO

Lista de novas substâncias psicoativas

FENILETILAMINAS E DERIVADOS

1) 1-Fenilpropanamina (1-fenilpropilamina)

DERIVADOS DA CATINONA

57 2-Metilmethcathinona

159) Cetamina ((RS)-2-(2-Clorofenil)-2-(metilamino) ciclohexanona)
2. Cathinones

text as in Hungarian legislation

2. Those compounds containing a cathinone (2-amino-1-phenylpropane-1-one) structural part – with the exception of bupropion –,

in which the

2.1 carbon atom at position 3 of the propane-1-one structural unit may contain
   2.1.1 an alkyl group of up to 3 carbon atoms

2.2 phenyl group may contain one or – in any optional combination – more
   2.2.1 halogen atom, or methyl, ethyl, methoxy or methylenedioxy group

2.3 nitrogen atom
   2.3.1 may contain one or two alkyl group of 1–4 carbon atoms or
   2.3.2 may contain a benzyl group or
   2.3.3 is a member of a pyrrolidine or piperidine ring
Example: 2. Cathinones

graphical description (not shown in legislation)

- One or more substituents: H, CH₃, C₂H₅, OCH₃, F, Cl, Br, I
- Additional substituents: H₂C(=O)O⁻ and/or H₂C(=O)O⁻

- H or CₙH₂n+₁ (where n = 1–4)
- CₙH₂n+₁ (where n = 1–4), or
- - if the other substituent is hydrogen atom – CH₂Ph

- Exception: bupropion

  \[
  \text{Cl} \quad \text{H} \quad \text{N} \quad \text{C(CH₃)₃}
  \]

  \[
  \text{CH₃}
  \]

  \[
  \text{H} \quad \text{N} \quad \text{C(CH₃)₃}
  \]
EDND – unique and up-to-date data repository

- Unique data repository – unique reference source for forensic scientists
- Password protected – accessible only to EWS partners, sensitive data
- Widely used by forensic scientists, researchers, law enforcement and health care professionals and policy makers
- Low cost and shared investment
- Timely (real time) information – updated every day

Figures

- 454 new psychoactive substances
- 1111 analytical datafiles (including Chemstation datafiles, FTIR and NMR)
- 1660 scientific publications
- 2116 Reporting Forms
- 2465 national control status updates
Identification challenges
what is required for the unequivocal identification of a NPS?

- Lack of reference standards
- Analytical equipment
- Development and validation of methods
- Quantitative (sensitivity) vs qualitative (selectivity) analysis
- Target (screening) vs non-target (discovery) methods

And… additional difficulties for identifying NPS in biological samples!

- Identification of isomers, stereoisomers
- Mixtures of substances in different amounts (polydrug use)
- Lack of formal pharmacokinetic/pharmacodynamic studies & extrapolation of \textit{in vivo} results from animal models – unknown metabolites, large number of potential metabolites, same metabolite may be a marker for different parent compounds
- Short vs long-term detection
- Analysis of biological material by NMR is difficult (low concentrations, matrix effects, etc.)
- Unknown toxic / fatal / legal thresholds for NPS
Thank you for your attention

http://www.emcdda.europa.eu/about/partners/reitox-network