Emerging Trends in New Drugs in the European Union

Andrew Cunningham, Scientific Analyst
NIST/DEA Emerging Trends in Synthetic Drugs Workshop,
30 April 2013
Overview

EU Early warning system
Fundamental shift in the drugs market
Diversity of new drugs - monitoring in action
Concerns - getting new drugs in perspective
What next?
EWS institutional partners

- European Monitoring Centre for Drugs and Drug Addiction
- Reitox Focal Points
- Europol National Units
- Pharmacovigilance system
Council Decision 2005/387/JHA

I. Information exchange
   Early warning system (EWS)

   EWS guidelines

II. Risk assessment

   Risk assessment guidelines

III. Decision-making

   Council Decisions on control

European Database on New Drugs (EDND)

Risk assessment new psychoactive substances

- Formalized guidelines
- Health risks, Social risks, Organized crime
- Diffusion potential

- MBDB (1998) — not controlled EU
- 4-MTA (1999) — controlled EU
- GHB (2000) — controlled UN
- Ketamine (2000) —
- PMMA (2002) — controlled EU
- 2C-I, 2C-T-2, 2C-T-7, TMA-2 (2003) — controlled EU
- BZP (2007) — controlled EU
- Mephedrone (2010) — controlled EU
- 4-MA (2012) — proposal for control EU
- 5-IT (2013) — risk assessment held April 2013
EWS: Triangulation of information from different sources

Internet, media, users

Research, test purchase, wastewater analysis, QSAR modelling

Forensic data/toxicology, law enforcement, surveys, health & care

European Database on New Drugs

emcdda.europa.eu
• Real time information
• Low cost
• Shared investment & shared benefits
Fundamental shift

Gary L. Henderson, Ph.D.

Designer Drugs: Past History and Future Prospects


Future Trends

In the view of this author, it is likely that the future drugs of abuse will be synthetics rather than plant products. They will be synthesized 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.
The challenge we face today — has it changed?

U.S. Drug Sleuths Finally Solve Mystery of the Deadly China White

New Narcotic Identified After Monthlong Quest

As Federal drug agents and California police stepped up their search for the sources of the China White, the forensic chemists turned their detection scales to a backlog of other, more routine cases. The challenge of identifying a new drug from the street comes no more than once or twice a year.
Substances reported via the EWS

Joint action 97/396/JHA
(June 1997 – May 2005)
~ 30 notifications

Council Decision 2005/387/JHA
(May 2005 – 2012)
~ 230 notifications

Increasing number & quality of reports received

Reporting forms received
New notifications
236 new drugs notified since 2005

More than 280 monitored since the EWS started

Synthetic cannabinoids, phenethylamines and cathinones most common

More diverse and obscure substances being reported

Many more substances offered for sale that have not yet been identified by chemical analysis
What is driving this?

A complex web...

Globalisation and advances in information technology, internet as:
- Communication tool
- Access to information (medicinal chemistry, patents, etc., etc)
- Global market place

Available and cheaper organic synthesis capacity
- ‘legally’ sourced often outside Europe
- limited regulation/enforcement: availability on the open market
- differences in national laws
What is driving this?

A complex web…

Innovative marketing of products within a ‘grey’ regulatory zone

Changes in illicit drug market and interaction between markets

  Gaps in availability (such as poor quality of illicit stimulants or heroin drought?)
  Interaction between the markets in illicit drugs, 'legal highs' and medicines
  Creation of new drug markets

Users willing experiment… and substitute
Responding to new marketplace

‘Specialist’ shops
  Responses have been quite successful (IE, PO)

Internet
  A challenge!

The illicit marketplace
  Controlled and non-controlled NPS increasingly present
  Some evidence manufacture in illicit labs
  Interaction with other synthetic drugs and stimulants
  Internet and dark web
693 online shops identified selling to the EU in 2012
Up from 314 in 2011 and 170 in 2010

Other features of the online market include:

Legal highs may not be legal

Open market
  dietary supplements, lifestyle and self-medication products (e.g. phenibut, DMAA)

Developments:
  Spamdexing, diversification, & more covert strategies
Monitoring internet may also be important for understanding trends.

‘Mexican seafood’ was asking about spice back in 2006 and ‘mad scientist’ told him that we did not know.

It took another 2 years to confirm the nature of the ingredients.
The emergence of synthetic cannabinoids

First CRA in a smoking mixture sold as ‘Spice’ was JWH-018
First detected (analytically confirmed) in Europe, Dec. 2008
Now, EWS monitors more than 70 CRA’s
Notified to EMCDDA in June 2012

Stimulant type drug (little known)

Sometimes sold as ‘Benzofury’ which has contained different drugs in the past (e.g. 5/6-APB).

Users may think they are taking a different drug

Analytical difficulties (cf. AMT)

24 deaths in 4 MS linked to the drug
**N-2-methoxybenzyl derivatives of the ‘2C-series’ of phenethylamines**

Extremely potent, active at μg level

Binding affinities at 5-HT2A receptors Ki 0.16–1.49nM

Typically detected in ‘blotters’/tabs, sugar cubes

<table>
<thead>
<tr>
<th>Phenethylamine</th>
<th>-NBOMe derivative</th>
<th>Date</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C-B</td>
<td>25B-NBOMe</td>
<td>Dec-12</td>
<td>Sweden</td>
</tr>
<tr>
<td>2C-C</td>
<td>25C-NBOMe</td>
<td>Jun-11</td>
<td>Finland</td>
</tr>
<tr>
<td>2C-D</td>
<td>25D-NBOMe</td>
<td>Apr-12</td>
<td>UK</td>
</tr>
<tr>
<td>2C-E</td>
<td>25E-NBOMe</td>
<td>Dec-12</td>
<td>Poland</td>
</tr>
<tr>
<td>2C-G</td>
<td>25G-NBOMe</td>
<td>Dec-12</td>
<td>Poland</td>
</tr>
<tr>
<td>2C-I</td>
<td>25I-NBOMe</td>
<td>Jun-12</td>
<td>Sweden</td>
</tr>
<tr>
<td>2C-N</td>
<td>25N-NBOMe</td>
<td>Dec-12</td>
<td>Poland</td>
</tr>
</tbody>
</table>
Information sources – The challenges

Speed of developments
- Increase in the number, type and availability
- More diverse, obscure compounds
- Products, mixtures and mislabelling (licit & illicit)

Forensic capacity limited, analytic challenges
- Lack of reference standards
- Increasing numbers of mixtures
- Difficulties in identification (don’t know what you’re looking for)

Epidemiological challenges
- Self-reported data becoming increasingly less useful
- Mislabelling of products, change of composition over time and region
- Lack of standardised questions, common definitions and agreed terminology

Integrate more innovative & proactive monitoring approaches
- Waste water
- Test purchasing
- Internet monitoring
- Computational studies
Better conceptual models to understand diffusion potential

Need to develop hospital emergency data

Increase capacity to respond rapidly to particularly toxic products – rapid and sound assessment of properties & risks
- Identification of DID associated with NPS
- Evaluation of potential acute and chronic toxicity in humans
- Receptor binding and mode of action studies
- Assessment of psychoactivity

Follow – up over time important
- Re-emergence of controlled drugs and establishment on the licit market
What next?

Synthetic cannabinoids, not yet detected in Europe, e.g.

*N. Uchiyama et al./Forensic Science International xxx (2012) xxx–xxx*

5-Fluoropentyl-3-pyridinoylindole (III)

$C_{19}H_{19}FN_2O$: 310
What next?

Dhooper, H. K., (2010), *Opioid-cannabinoid co-drugs with enhanced analgesic and pharmacokinetic profile*, University of Kentucky, KY

**Codeine-Δ⁹-Tetrahydrocannabinol Carbonate.**
What next?

Synthetic ‘co-drugs’


Reaction product of URB-754 with 4-Methylbuphedrone (II)

C_{28}H_{31}N_{3}O_{3}: 457
Let’s see!

andrew.cunningham@emcdda.europa.eu