European Monitoring Centre
for Drugs and Drug Addiction

European Early warning system (EWS) on new drugs

Roumen Sedefov, Action on New Drugs

Workshop Information & Communication Technology per i Sistemi delle Dipendenze

Verona, 13-14 April 2010

Countries monitored by the EMCDDA:

27 EU Member States, Croatia, Turkey & Norway



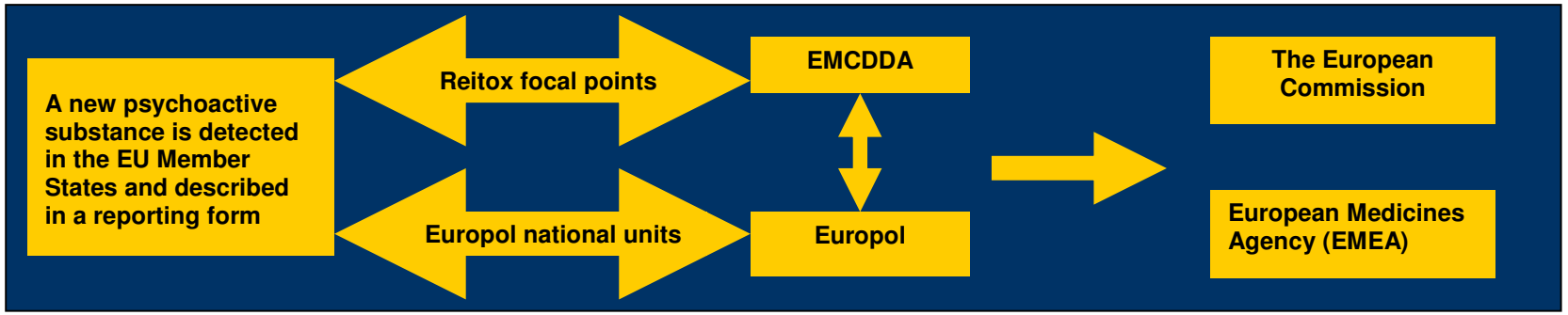


Outline

- European Early warning system (EWS)
  - New substances notified via the EWS in 2009
- A concept in development
  - 'Research chemicals'
  - 'Herbal'/'Legal' highs
  - Synthetic compounds (piperazines, levamisole, etc.)
  - 'Spice'
  - Synthetic cathinones
    - Mephedrone / Joint Report on mephedrone
- New risk assessment guidelines
- Challenges / anticipating the future

Council Decision 2005/387/JHA: a three-step process

Information exchange/Early-warning



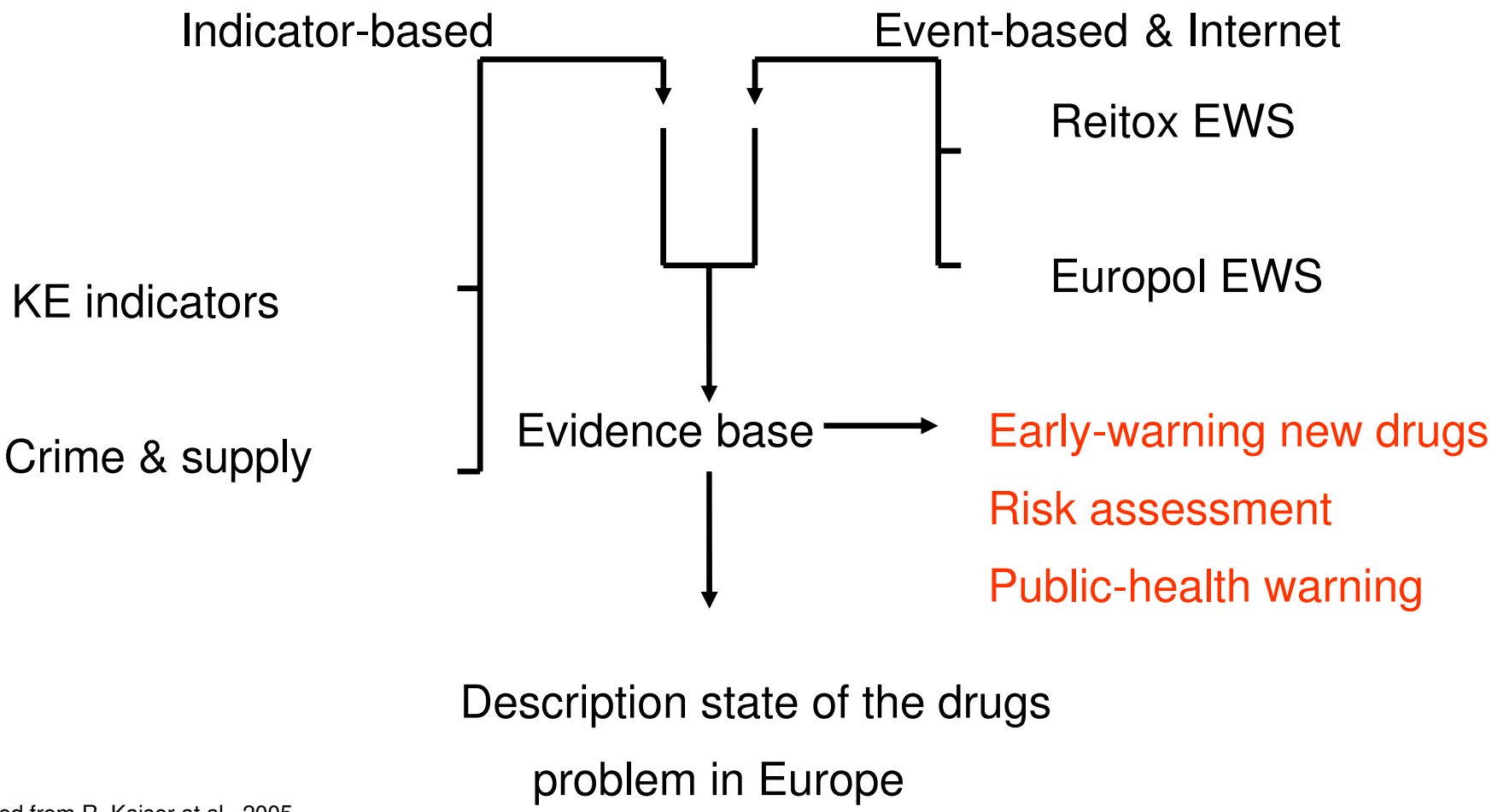
Risk assessment



Decision-making



EMCDDA monitoring system: sources and output



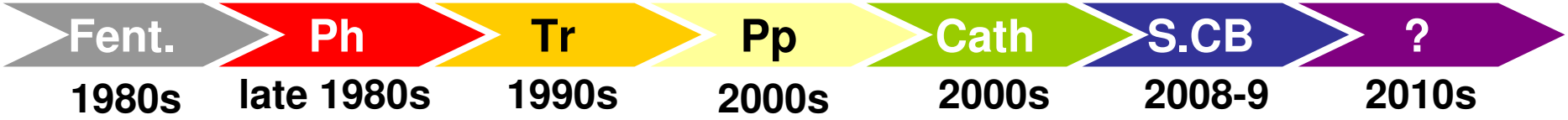
Adapted from R. Kaiser at al., 2005

24 New substances notified via the EWS in 2009

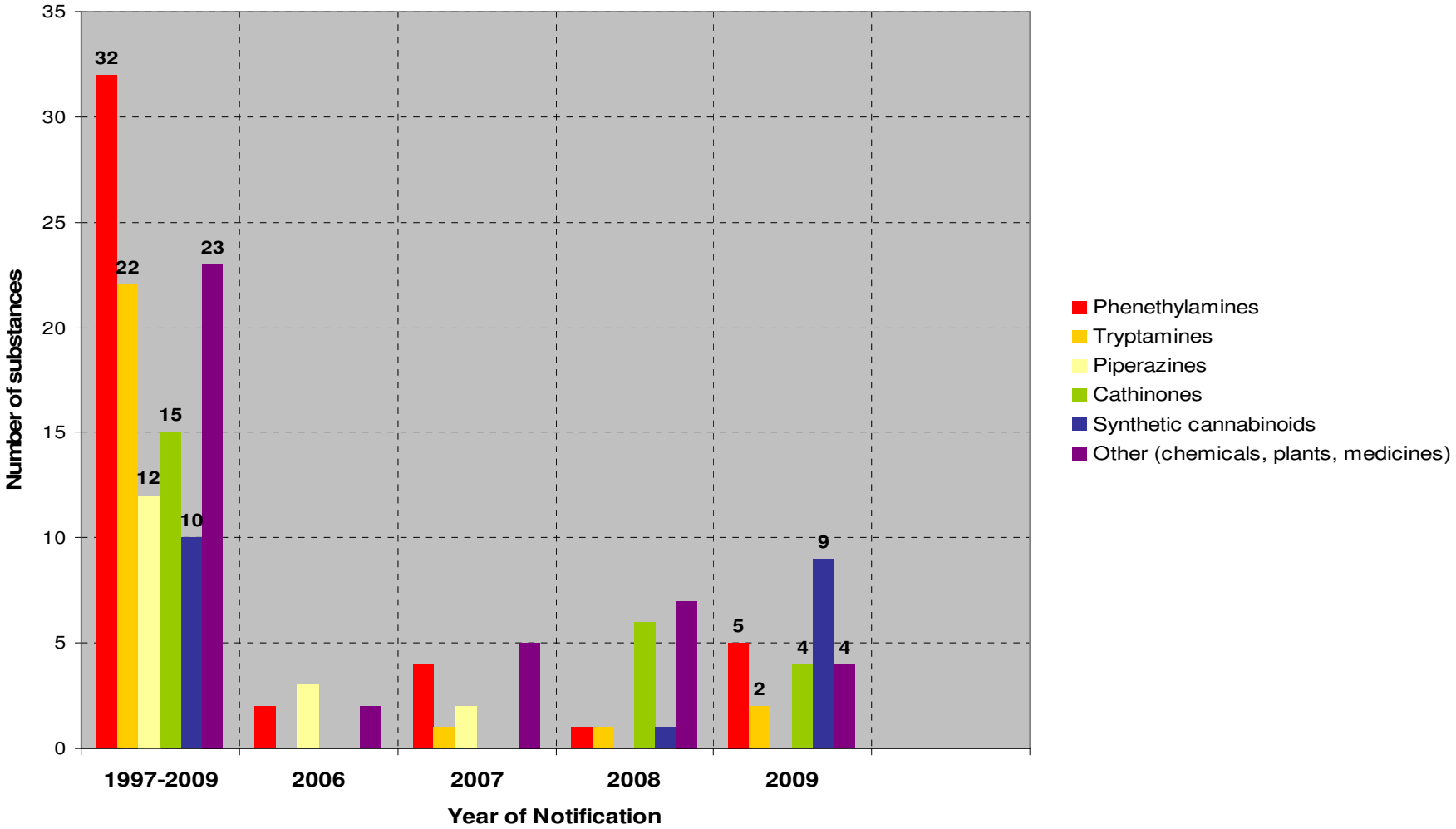
1. ***m*-fluoromethamphetamine** – 8 January 2009 – Belgium
2. **PPP** (α-pyrrolidinopropiophenone) – 27 January 2009 – Denmark; and 2 February 2009 – Finland
3. **2-DPMP** (2-diphenylmethylpiperidine) – 2 February 2009 – Finland
4-7. **CP 47,497 and its C6, C8 and C9 homologues** (5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol) – 23 February 2009 – Germany
8. **JWH-073** (1-butyl-3-(1-naphthoyl)indole) – 6 March 2009 – Denmark
9. **4-AcO-MET** (4-acetoxy-N-methyl-N-ethyltryptamine) – 24 April 2009 – Finland
10. **TMA-6** (2,4,6-trimethoxyamphetamine) – 3 June 2009 – Denmark
11. **HU-210** (1,1-dimethylheptyl-11-hydroxytetrahydrocannabinol) – 22 June 2009 – United Kingdom
12. **ODT** (o-desmethyltramadol) – 26 June 2009 – Germany
13. **4-AcO-DMT** (4-acetoxy-N,N-dimethyltryptamine) – 17 August 2009 – Finland
14. **2-PEA** (2-phenethylamine) – 2 October 2009 – Finland
15. **JWH-398** (1-pentyl-3-(4-chloro-1-naphthoyl)indole) – 6 October 2009 – United Kingdom
16. **JWH-250** (1-pentyl-3-(2-methoxyphenylacetyl)indole) – 6 October 2009 – Germany
17. **bk-PMMA** / **methedrone** (4-Methoxymethcathinone) – 12 October 2009 – Sweden
18. **Etaqualone** (3-(2-ethylphenyl)-2-methyl-quinazolin-4-one): – 12 November 2009 – Denmark
19. **MDPPP** (3',4'-methylenedioxy-α-pyrrolidinopropiophenone) – 12 November 2009 – Denmark
20. **Metamfepramone** (N,N-dimethylcathinone) – 12 November 2009 – Denmark
21. **3-FMA** (3-fluoromethamphetamine) – 17 November 2009 – Finland
22. **JWH-200** (1-[2-(4-morpholino)ethyl]-3-(1-naphthoyl)indole) – 3 December 2009 – Lithuania
23. **4-MA** (4-methylamphetamine) – 14 December 2009 – Belgium
24. **Pregabalin** ((S)-3-(aminomethyl)-5-methylhexanoic acid) – 16 December 2009 – Finland

24 New substances notified via the EWS in 2009

- 5 Phenethylamines
  - 2FMP or 3FMP, 2-PEA, TMA-6, 3-FMA and 4-MA
- 4 Cathinone derivatives
  - PPP, MDPPP, methedrone/bk-PMMA and metamfepramone
- 2 Tryptamines
  - 4-AcO-MET, 4-AcO-DMT
- 2 Medicinal products
  - Etaqualone and pregabalin/Lyrica
- Narcotic analgesic: ODT
- Other: 2-DPMP
- Piperazines: none
- Plants: none



Number of substances notified to the EWS by year and group



A concept in development

- Designer drugs
- ‘Research chemicals’
- ‘Herbal’ / ‘Legal’ highs
- Synthetic compounds
  - Piperazines – party pills
  - Levamisole
- ‘Spice’
- Synthetic cathinones
  - Mephedrone

- Not dealt with here: smart drugs (*per se*), body and image enhancers, nutritional supplements

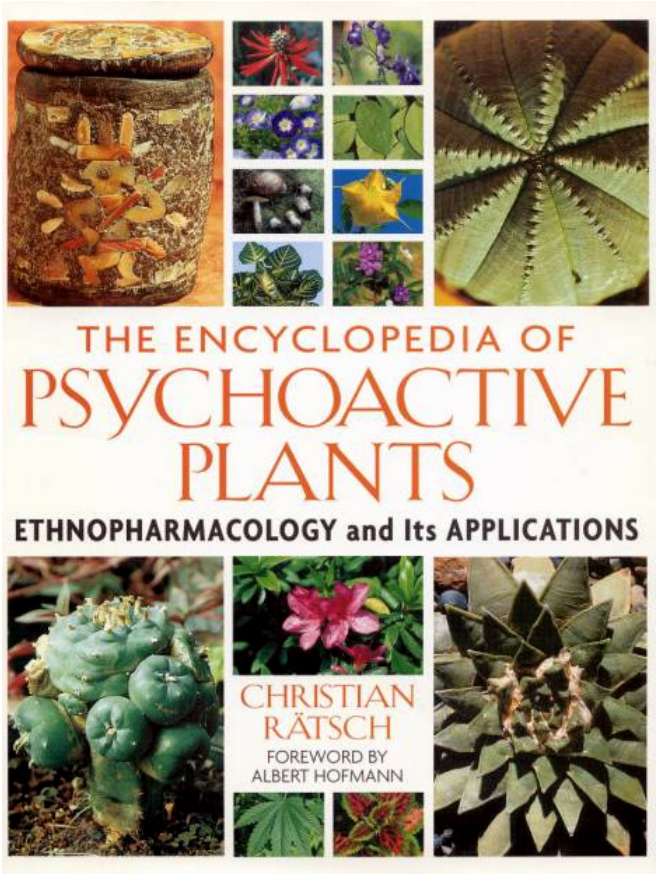
Research chemicals?



Source: Michael Bovens, ENFSI Drugs working group

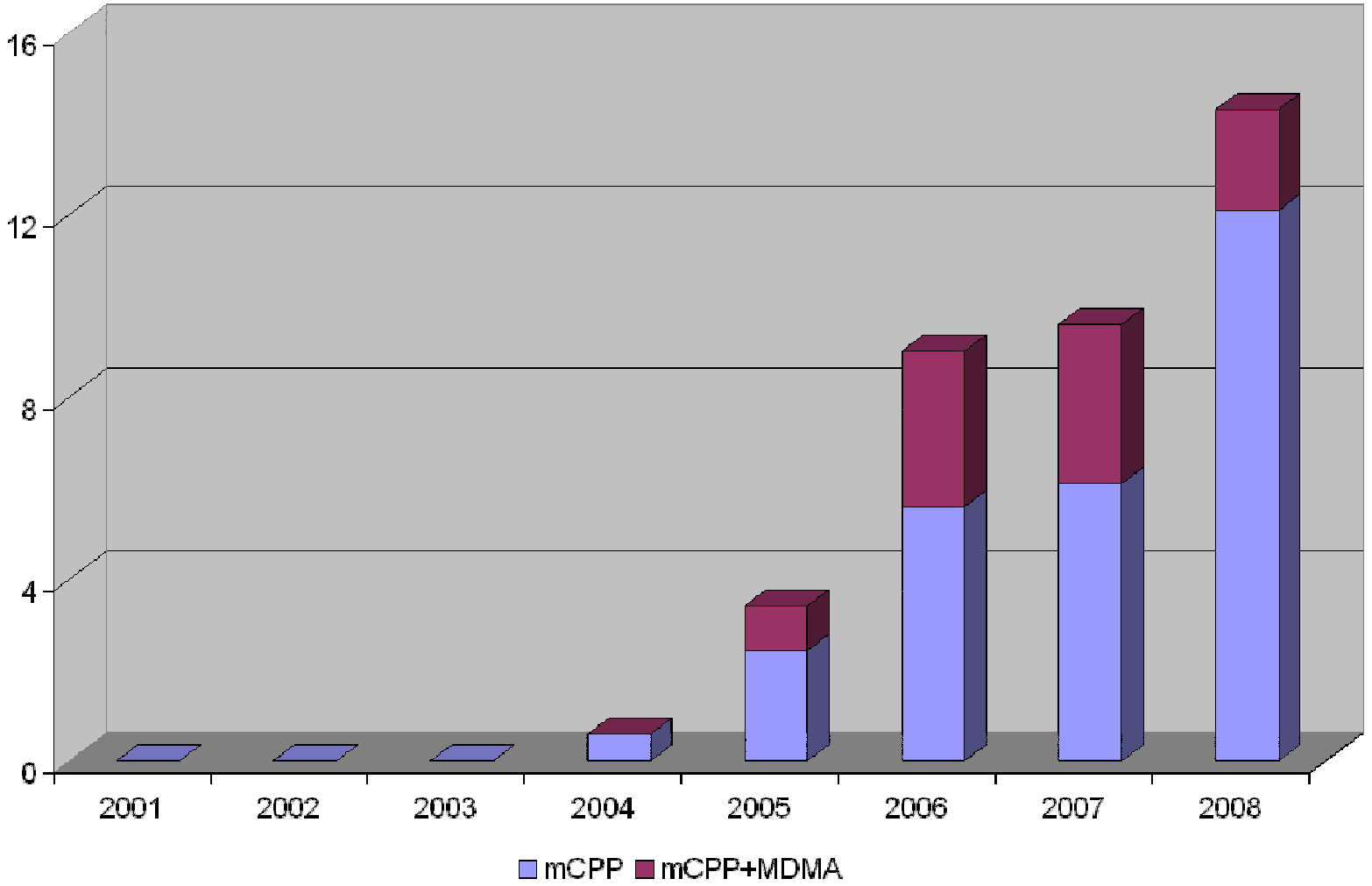
‘Herbal highs’ – herbal and plant materials

- *Salvia divinorum* (Mexican Sage) – salvinorin A
- *Mitragyna speciosa* (Kratom) – mitragynine
- *Piper methysticum* (Kava) – kavalactones
- *Argyreia nervosa* (Hawaiian Baby Woodrose) - lysergamide



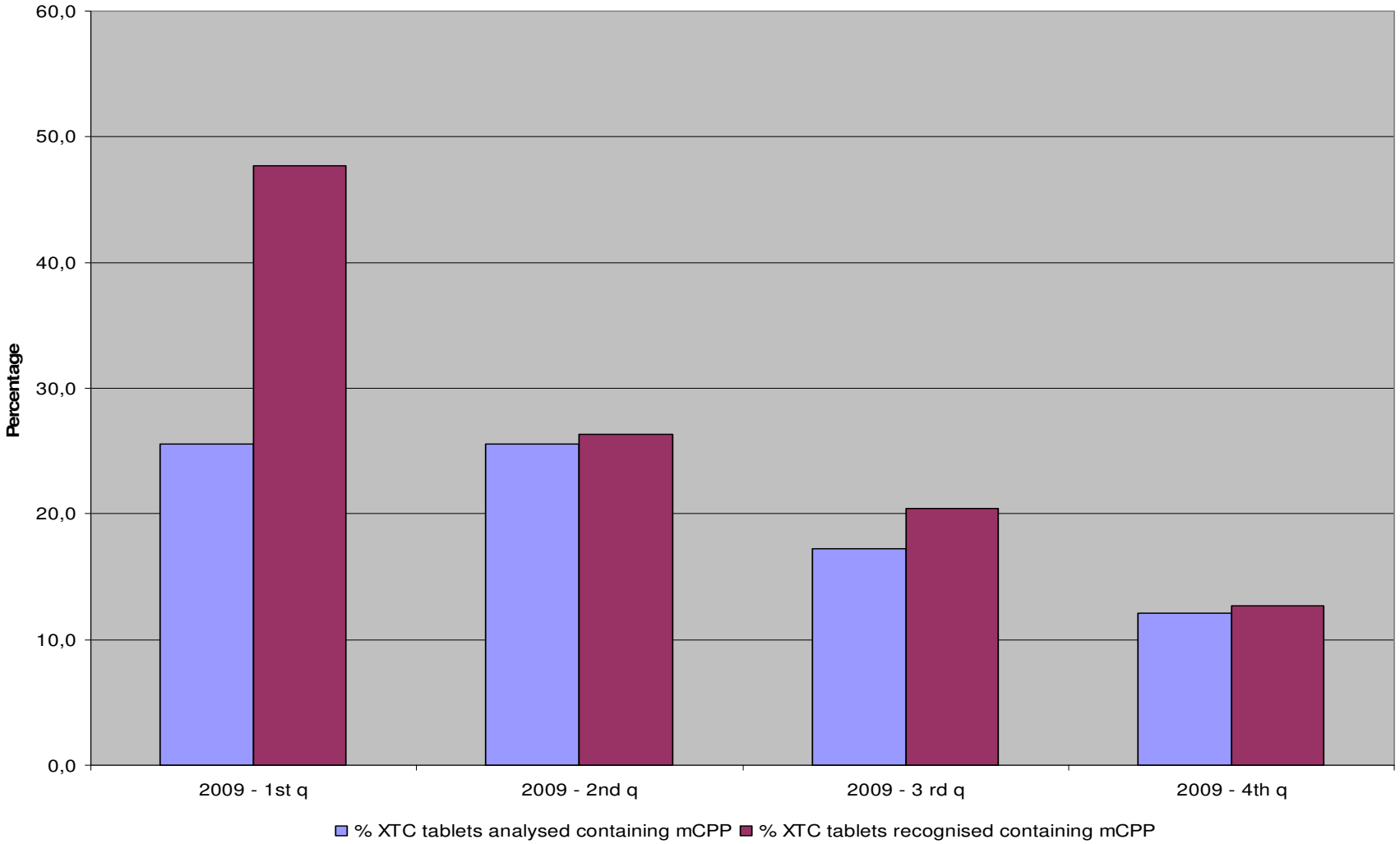
Piperazines (1)

Drugs Information and Monitoring System, the Netherlands



Piperazines (2)

Drugs Information and Monitoring System, the Netherlands



Levamisole – warning and survey

- Levamisole is an adulterant of cocaine, not routinely identified and only rarely quantified
- In 2009, over 70% of cocaine seizures that were analysed in the US contained levamisole
- In 2009, the EWS issued a public health warning and a survey
  - — Information sources: national toxicology, forensic science and custom services
  - — Increase in the percentage of cocaine samples adulterated with levamisole: 1/3 (Belgium, France, Spain and Sweden) and 1/2 of the cocaine seizures analysed (the Netherlands, Ireland and the UK) contained levamisole
  - — Increase in the concentration of levamisole in cocaine samples
- Levamisole may cause a number of adverse effects, of which agranulocytosis is the most alarming

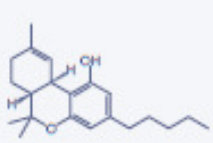
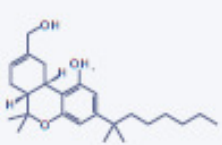
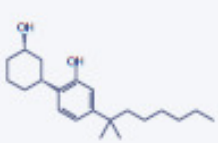
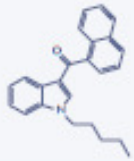
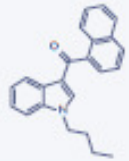
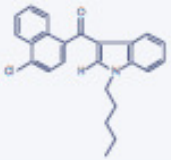
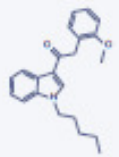
The story of Spice…

- Herbal mixtures sold on the Internet (mainly), but also specialised shops
- An ‘exotic incense blend’, ‘not for human consumption’
- Reported by some users to have effects similar to cannabis.
- Extensive forensic investigations DE, AT: JWH-018 & CP 47,497
- Control measures: AT, DK, EE, FR, DE, LT, LU, LV, PL, RO, SE, UK, etc
- New cannabinoids continue to appear



Synthetic cannabinoids reported via the EWS so far

Δ⁹-THC and six synthetic cannabinoids with high affinity for cannabinoid (CB_1) receptors found in 'Spice' products

	Δ⁹-THC	HU-210	CP 47,497	JWH-018	JWH-073	JWH-398	JWH-250
Family/group	Naturally occurring dibenzopyran	'Classical' cannabinoid (dibenzopyran)	Cyclohexylphenol	Naphthoylindole	Naphthoylindole	Naphthoylindole	Phenylacetylindole/ benzoylindole
Subgroup	Tricyclic terpenoid derivative with a dibenzopyran ring	Δ⁹-THC analog	ACbicyclic cyclohexylphenol	1-alkyl-3-(1-naphthoyl) indole	- 1-alkyl-3-(1-naphthoyl) indole	3-(4-halo-1-naphthoyl) indole	1-pentyl-3-phenylacetylindole
Structure							
Potency and selectivity	Reference. Partial agonist at CB_1	Full non-selective agonist at CB_1/CB_2	Potent selective CB_1 agonist	Very potent selective CB_2 agonist (also potent CB_1 agonist)	Potent selective CB_1 agonist (also weaker CB_2 agonist)	Very potent non-selective CB_1/CB_2 agonist	Potent selective CB_1 agonist (also weaker CB_2 agonist)
Binding affinity for CB_1 _Ki [nM] (Advisory Council on the Misuse of Drugs, 2009)	**10.2** (Advisory Council on the Misuse of Drugs, 2009)	**0.06** (Howlett et al., 2002)	**9.54** (Auwärter et al., 2009)	**9** (Huffman, 2009; Huffman et al., 2003)	**8.9** (Huffman, 2009; Huffman et al., 2003)	**2.3** (Huffman, 2009)	**11** (Huffman, 2009)
Synthesised by	Naturally occurring phytochemical	R. Mechoulam	Pfizer	J. W. Huffman	J. W. Huffman	J. W. Huffman	J. W. Huffman
First notified by	N/A	United Kingdom	Germany	Austria	Netherlands	United Kingdom	Germany
Control measures (as of 9/10/2009)	Internationally controlled	Austria, Estonia, France, Lithuania, Luxembourg, Sweden	Austria, Estonia, France, Germany, Lithuania, Luxembourg, Sweden	Austria, Estonia, France, Germany, Lithuania, Luxembourg, Poland, Sweden	Lithuania, Luxembourg, Sweden	—	—

JWH-200 reported on December by Lithuania and maybe more …

Spice story – Challenges

- Why did it take such a long time to establish the psychoactive principles in the Spice products?
  - Listing on the label of herbal components
  - Complex matrices of the extracts of the mixtures
  - Large amount of non-psychoactive compounds (vitamin E) to 'mask' the active components
  - Addiction of synthetic cannabinoids difficult to detect
- Are those products dangerous for the consumer?
  - Little is known about metabolism and toxicology of the synthetic cannabinoid compounds
  - The detection of metabolites in urine samples is not fully developed

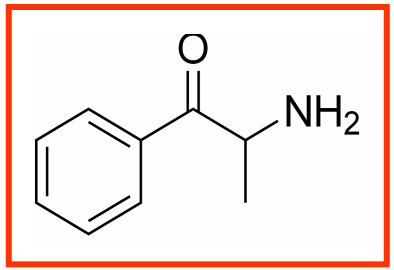
Spice story – Future

- In February 2009, **mytragynin** (the main psychoactive alkaloid of the plant Kratom) was identified in Austria
- Similarly, in June 2009, a metabolite of the synthetic opioid analgesic **tramadol** was found in Germany in an incense preparation called 'Krypton', advertised as a kratom-based product

It can not be excluded that substances from these or other chemical groups with a cannabinoid receptor agonist or other pharmacological activity could be added to any herbal mixture in the future

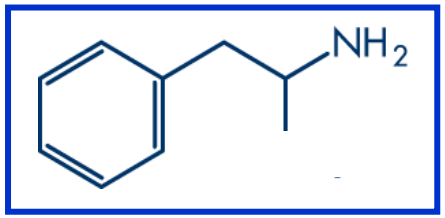
Cathinones: structural analogues of phenetylamines

Cathinones

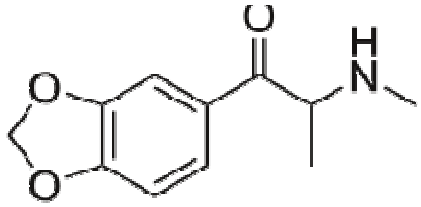


(Cathinone)

Phenetylamines



(Amphetamine)



Methylone

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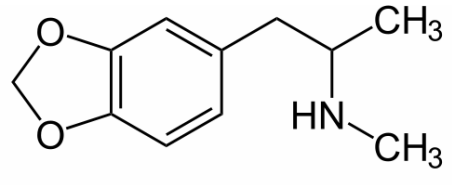
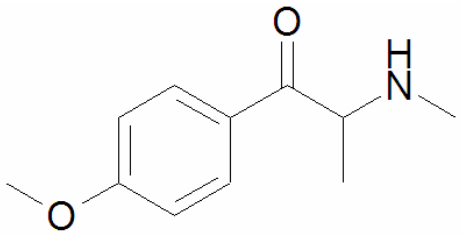


MDMA



Methedrone (bk-PMMA)

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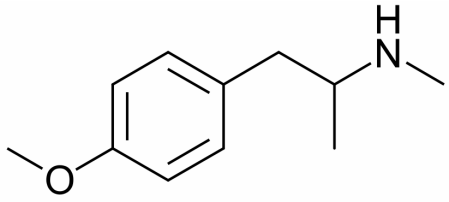


PMMA

www.emcdda

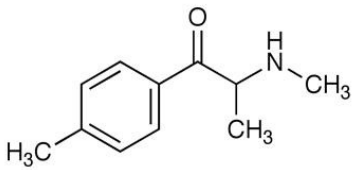
structurally-related analogues with
similar pharmacological profile

Cathinones sold as ‘legal highs’

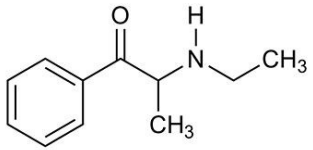
- First reported in 2005 – (methylone), sold as a ‘room odoriser’
- 6 cathinones were reported to the EWS in 2008
- 4 cathinones have been reported in 2009
- 15 cathinones are being monitored by the EWS



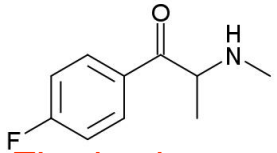
Notified to the EWS in 2008



Mephedrone



Ethylcathinone



Flephedrone

Joint Report on mephedrone

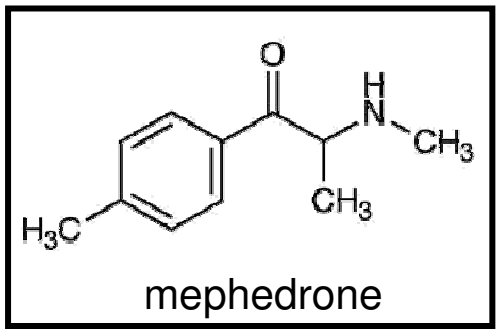
In January 2010, the EMCDDA and Europol examined the available information on mephedrone, through a joint assessment based upon the following criteria:

1. the amount of the material seized;
2. evidence of organised crime involvement;
3. evidence of international trafficking;
4. analogy with better-studied compounds;
5. evidence of the potential for further (rapid) spread; and
6. evidence of cases of serious intoxication or fatalities.

On 20 January 2010, a formal procedure to collect further information on the substance, in order to prepare a Joint Report, was launched in accordance with Art. 5 of Council Decision 2005/387/JHA

Mephedrone – chemistry

- Mephedrone is the common name for 4-methylmethcathinone
- It is a synthetic ring-substituted cathinone derivative



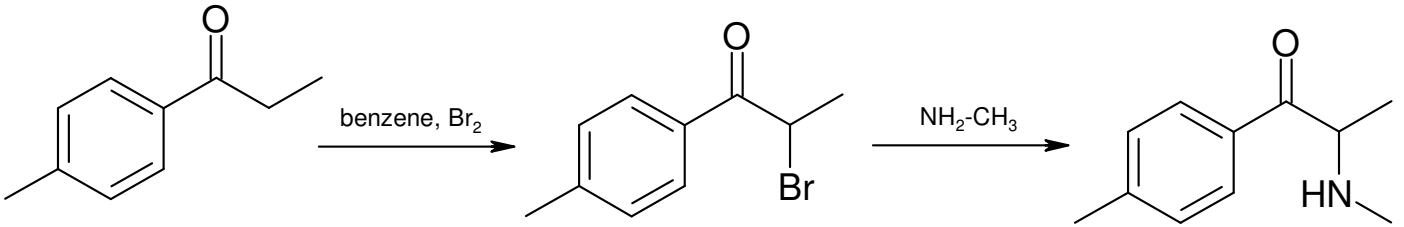
mephedrone



white, yellowish powder

- It was first detected in November 2007 and notified via the EMCDDA's Early Warning System in March 2008

- The main precursor of mephedrone is 4-methylpropiophenone



4-methylpropiophenone

4-methylbromopropiophenone (intermediate)

mephedrone

Availability

- Mephedrone is legally available over the **Internet** where it can be bought in retail quantities or in bulk
- A targeted Internet search in English identified:
  - 31 online shops in December 2009
  - 78 online shops in March 2010

  most of them were mephedrone-dedicated and based in the UK

  the retail price for one gram was around 12 GBP

- In some Member States users may source mephedrone from:
  - **specialised shops** (head/smart shops)
  - **street level** drug dealers
- The main precursor of mephedrone (4-methylpropiophenone) is also available on the Internet

Google search







(c) Nelson Pombeiro/EMCDDA

Marketing strategy

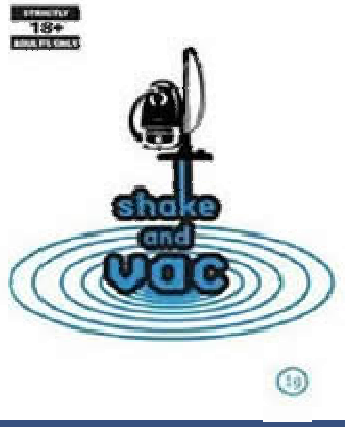
meph, drone, bubble
meow meow, miaow miaow
bounce, subcoca, M-CAT, 4-MMC

- Aggressively marketed by various online suppliers as a ‘legal-high’ – a legal alternative to ecstasy or cocaine
- On the Internet, mephedrone is advertised as a ‘research chemical’, 'bath salts', ‘for botanical research’, ‘plant food’, ‘plant feeder‘, ‘hoover freshener’, etc. often with a note indicating that it is 'not for human consumption'. There is often no indication of the presence of psychoactive substances in the list of ingredients of the marketed products. There are, however, online shops which are explicit about the actual usage of mephedrone









Media coverage

—EMCDDA has collected more than 300 media articles from January 2010 to March 2010, most of them from the United Kingdom popular press

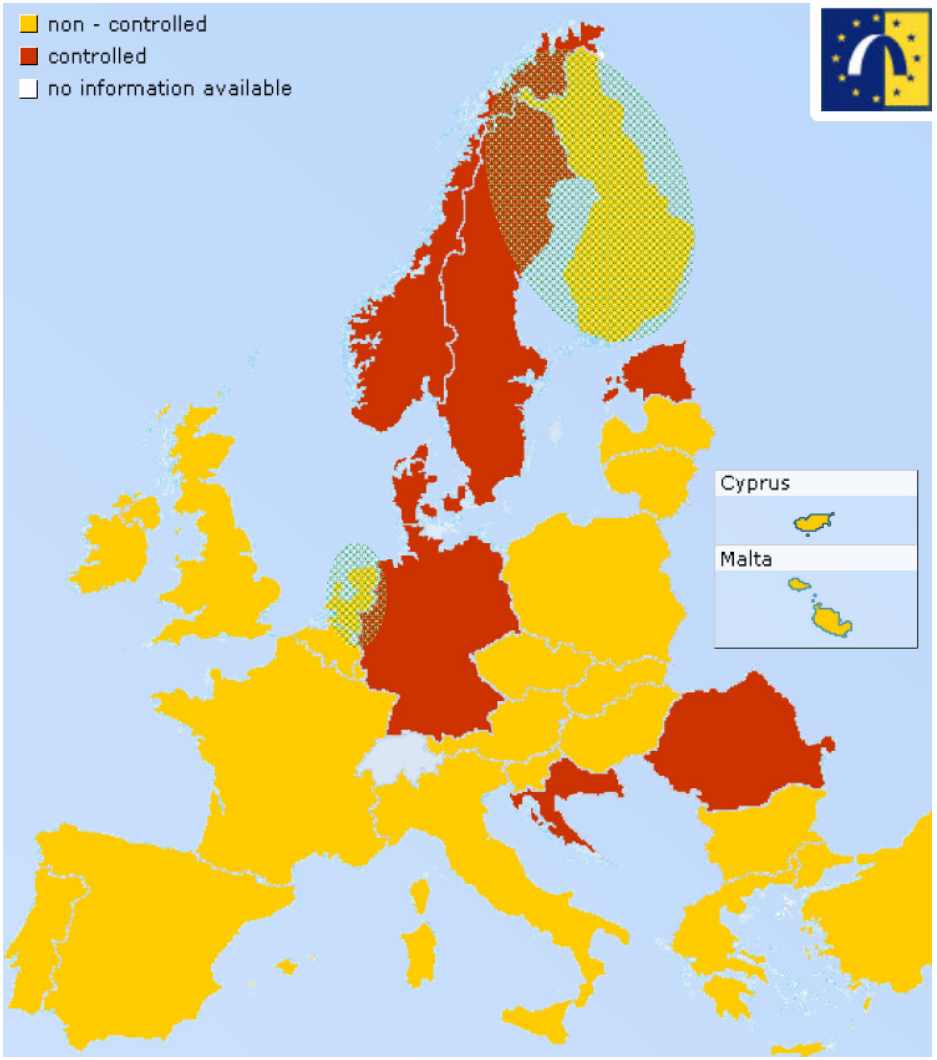
—There is anecdotal evidence that increased media coverage of mephedrone may have lead to an increased general population and user awareness about the substance

—Also in: users forums, blogs, etc

Control measures

— Five Member States (Denmark, Germany, Estonia, Romania and Sweden) as well as Croatia and Norway **control mephedrone under drug control** or equivalent legislation

— Two Member States (the Netherlands and Finland) regulate mephedrone under their **medicines-related legislation**



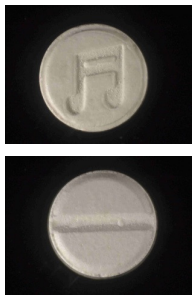
Other uses

- Mephedrone has **no known medical use** (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for mephedrone in the EU or in the Member States which responded to the **European Medicines Agency** (EMA). There is no information that mephedrone is used for the manufacture of a medicinal product in Europe

- Mephedrone is currently **not under assessment** and has not been under assessment by the **UN system**

- There are no indications that mephedrone may be used for other purposes

Encounters







- **Seizures**
  - —**Twenty Member States** as well as Croatia and Norway reported to Europol and the EMCDDA seizures of mephedrone in powder form or tablets, ranging from 2 grams up to more than 130 kilograms of mephedrone seized, the latter equalling approximately 260 000 tablets
  - —Five Member States indicate that legal production and distribution takes place from Asia and in particular China with one MS confirming such importation during 2008
  - —There are limited reports of crime and anti-social behaviour related to mephedrone use and supply
- **Collected samples**
  - —Six Member States (BE, CZ, FR, NL, AT, UK) reported samples collected and analysed for monitoring, research or prevention/harm reduction purposes

Belgium		Netherlands	
Croatia			
Slovakia		United Kingdom	

Drug users survey

- An online cross-sectional survey through a website associated with the specialist dance music magazine Mixmag carried out in late 2009 collected data from over 2000 respondents

- **Prevalence of use**

  mephedrone was the fourth most commonly used drug (after cannabis, ecstasy and cocaine) and the most widely experienced ‘legal high’, with 33.6 % of the respondents having tried it in the last month, 37.3 % in the last year and 41.7 % in their lifetime

Mode of use and effects

- **Route of administration:** oral ingestion and nasal insufflation (predominant) but also intravenous injection and rectal insertion
- **Dosage:** from 15 to 250 mg for oral ingestion and 5 to 125 mg for nasal insufflation. Users commonly report re-dosing during a single session with total doses typically being 0.5–1 g. Doses used in those presenting to healthcare services with acute toxicity range from 0.1–7.0 g.

Desired user reported effects*

comparable to that reported for MDMA, amphetamines and cocaine

(euphoria, general stimulation, enhanced music appreciation, elevated mood, decreased hostility, improved mental function and mild sexual stimulation)

Unwanted user reported effects*

—sweating (67 %)

—headaches (51 %)

—palpitations (43 %)

—nausea (27 %)

—cold or blue fingers (15 %)

* Source: Mixmag survey

Health risks and fatalities

- There are no published studies on the pharmacokinetics or pharmacodynamics of mephedrone in animals or humans
- There is detailed information available on the acute health effects associated with mephedrone toxicity from clinical case series. The acute health effects are similar to those seen with other stimulants
- Users report ‘craving’ in relation to mephedrone use which has the potential to lead to mephedrone dependency, and there are reports of mephedrone-dependence occurring
- Evidence of mephedrone use and associated toxicity has been increasing, in 2009 and 2010, particularly in the UK, where there are at least 14 reported cases in which mephedrone has either been detected in post-mortem samples or otherwise potentially implicated in death
- There has been only one confirmed death related solely to mephedrone in Sweden

Study to assess mephedrone health risks

- The EMCDDA has commissioned a contract to carry our telephone interviews among a unique pool of young recreational mephedrone users
- The structured interview will address the following assessment domains: demographics, use history, use, effects, risks and harms, and purchasing patterns
- In addition, all participants will be invited to send a urine sample for toxicological analysis to determine the precise cathinone compound(s) present after a recent use episode
- Quantitative toxicological assessments will be correlated with the self-reported dataset

Conclusion

The health and social risks caused by the use of, the manufacture of, and traffic in, mephedrone, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA

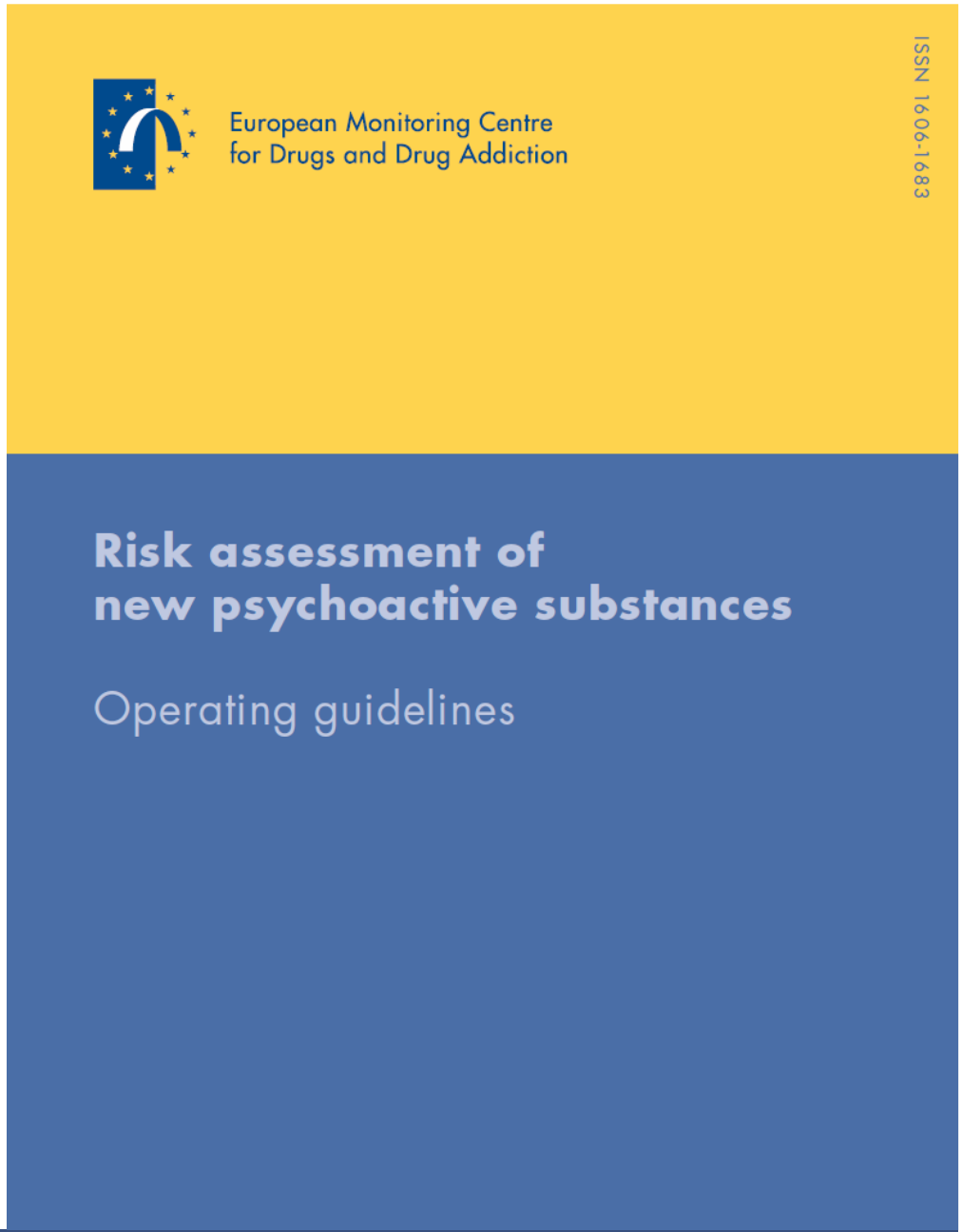
Next steps

	Deadline	N. of weeks	Week #
Launch	20-Jan	-	3
Information collected	03-Mar	6	9
EMCDDA-Europol Joint Report	31-Mar	4	13
RA requested	28-Abr	4	17
RA report	21-July	12	29
Total		26	

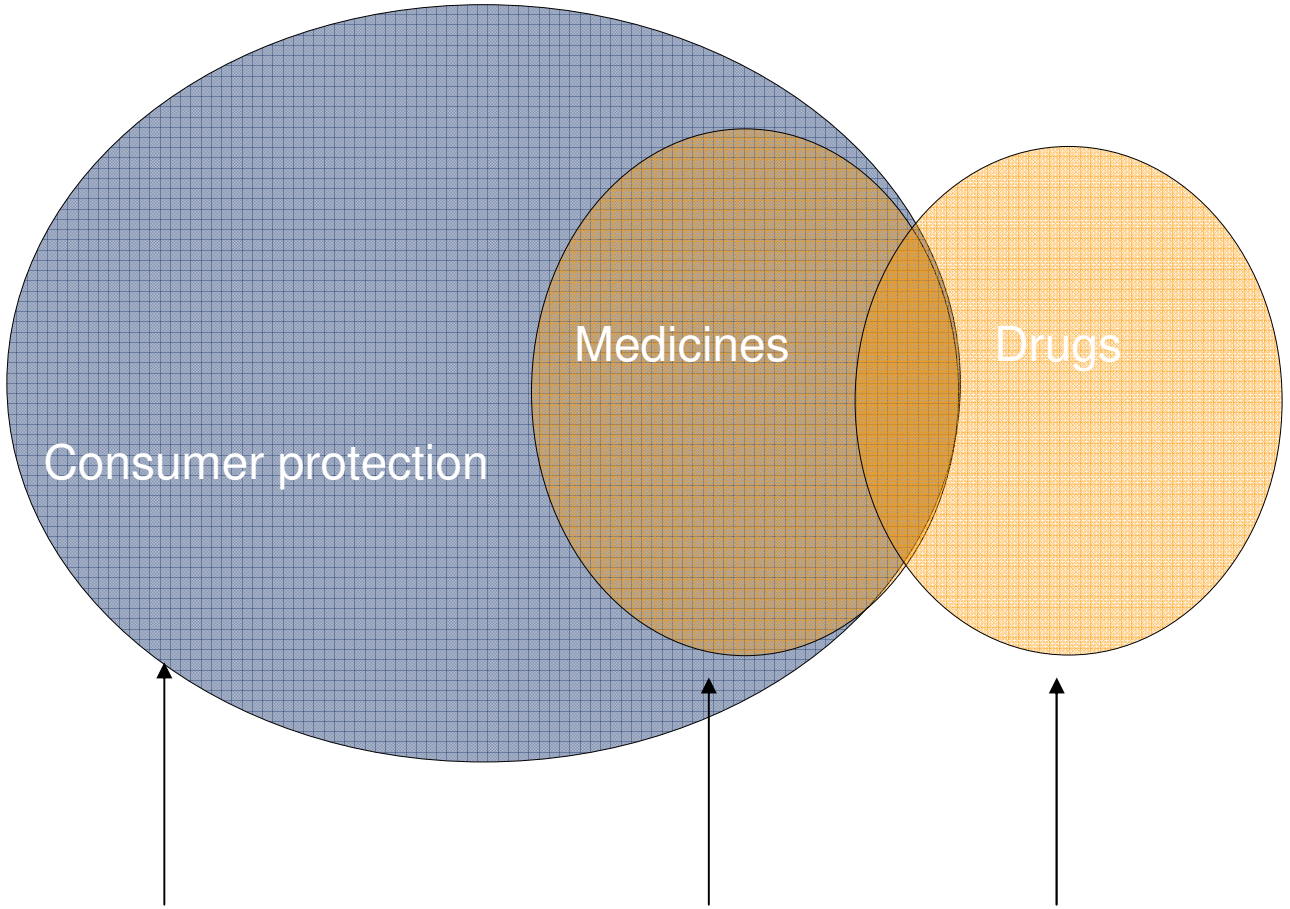
New risk assessment operating guidelines

- Considerations for risk assessment
- Conceptual framework for risk assessment
- Headings for the risk assessment report
- Semi-quantitative assessment procedure

Legal basis: Article 6 of Council Decision 2005/387/JHA



Challenges: what legislative response?



Anticipating the future

- In the context of fast technological advances, cheap organic synthesis and a global market, synthetic drugs are likely to grow in importance
- Herbal products, however, will continue to pose specific challenges
- Internet is likely to continue being the main vehicle

Acknowledgements

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