European Monitoring Centre for Drugs and Drug Addiction

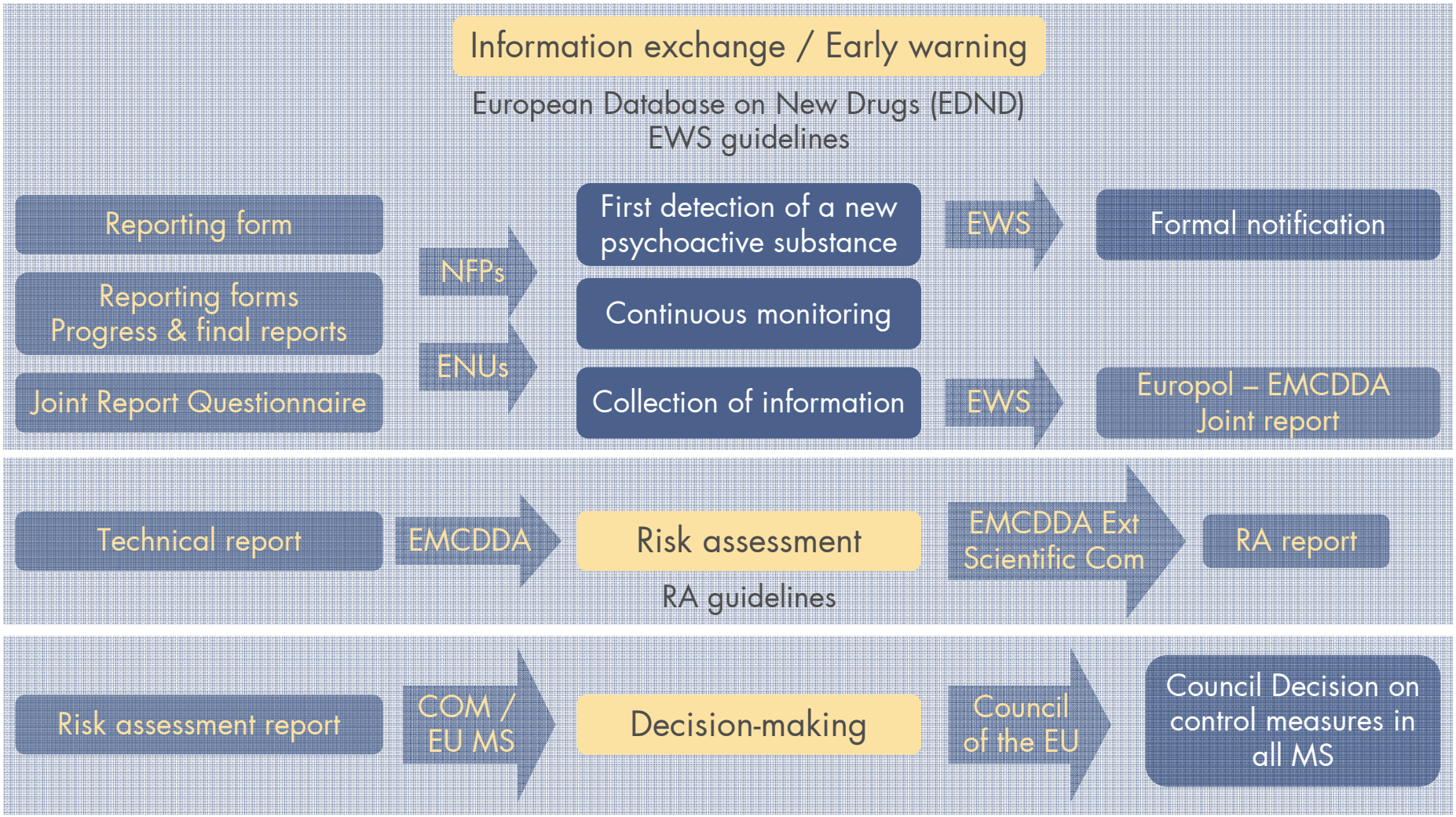
EU Early warning system on new psychoactive substances and new European trends

Roumen Sedefov, National EWS seminar, Zagreb, 19 April 2011

Challenge of rapidly changing legal highs market

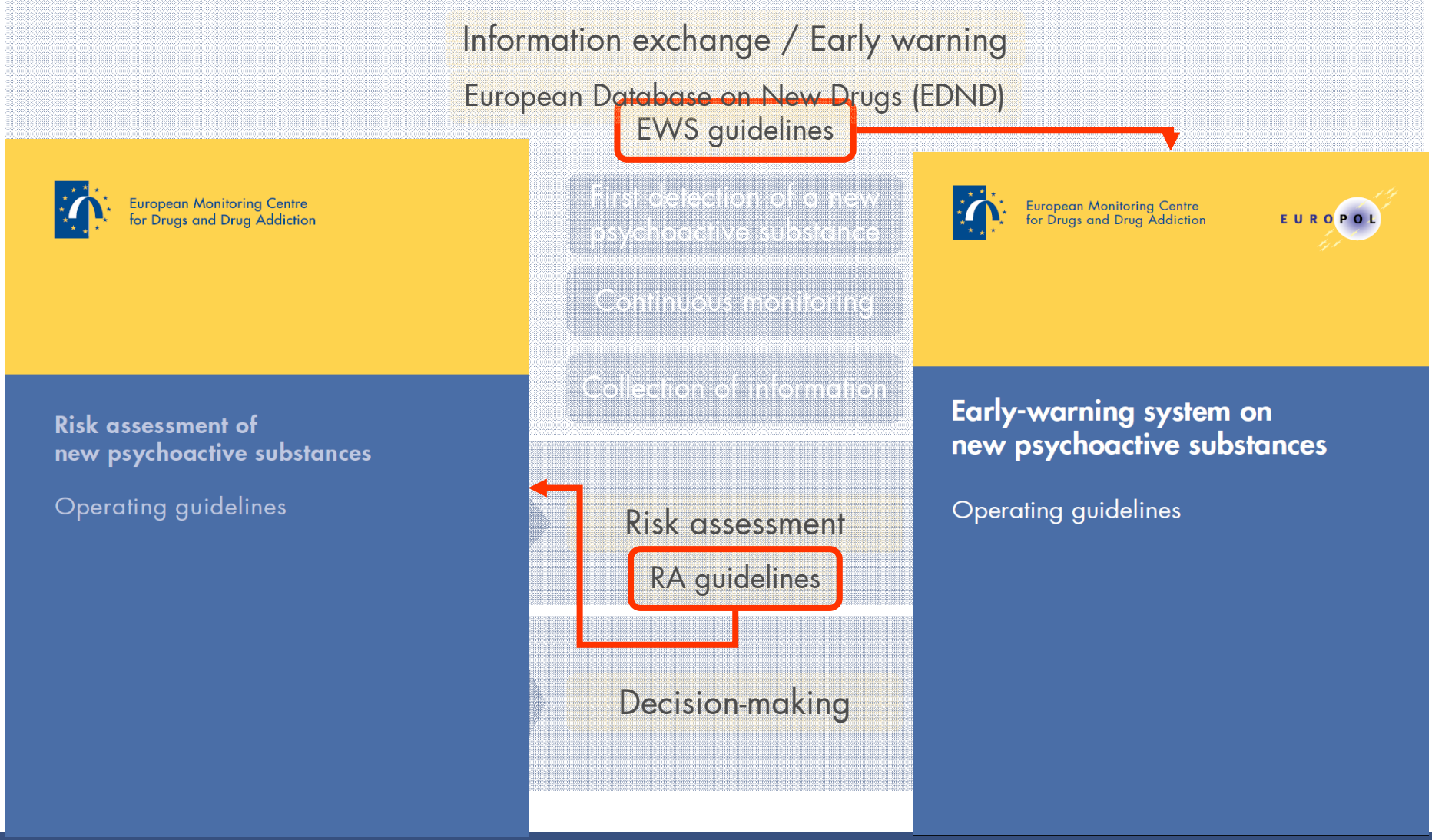
Council Decision 2005/387/JHA

EMCDDA – Europol annual report on implementation



Council Decision 2005/387/JHA

EMCDDA – Europol annual report on implementation



Tools – reporting forms

EWS

Risk assessment

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

Tools – biannual progress and final reports

EWS

Risk assessment

EARLY WARNING SYSTEM
Final report*/ Form

(In accordance with Council Decision 2005/387/JHA of 10 May 2005 on information exchange, risk assessment and control of new psychoactive substances)

MEMBER STATE....Estonia.....
DATE .09.07.10
PERIOD COVERED BY THE REPORT 01.01.10-01.07.10

New psychoactive substances identified during the period covered by this report

Substance	Physical description	Sample type	No. of cases	Total weight
(a) GHB	Liquid	S	14	4243
(a) Ketamine			0	0
(b) 2C-D (PIHKAL #23)			0	0

EWS

Risk assessment

Tools – European Database on New Drugs

EDND – European information system and database on new drugs

Substance: Naphyrone

Created
April 2010

Updated
July 2010

Type
Psychotropic substances

Group
Cathinones

Name
Naphyrone

Nature of substance
Naphyrone (naphthylpyrovalerone) is a synthetic cathinone, and a naphthyl analogue of pyrovalerone (internationally controlled under Schedule IV of the 1971 UN Conventions)

Systematic chemical name
Naphthylpyrovalerone

Other names
NRG-1, O-2482, Energy 1

Alerts

No alerts

Reports to EMCDDA

Ireland (Reporting Form): In June 2010 the NFP reported the identification of Naphyrone in collected samples of Pure NRG at Heads Shops. Samples also contained caffeine, lignocaine.

Sweden (Reporting Form): On 11 June 2010, the NFP informed on two seizures of powder of 10g and 288g, seized by the Swedish Customs. Both seizures involved two different persons but occurred on 18 April 2010.

Information from international partners

Information from EMEA
.

Information from other partners / institutions / countries
.

Assessment status in the UN system
.

EWS

Risk assessment

EDND – European information system and database on new drugs

Legal status

Click here to view an interactive map

United Kingdom: non-controlled

Naphyrone is not included in the generic definition of cathinone derivatives.

Chemistry

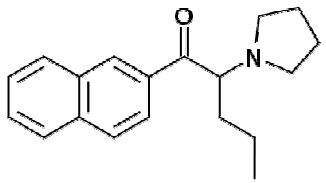
Other chemical names and variants
1-(2-naphthyl)-2-(1-pyrrolidinyl)-1-pentanone; 1-naphthalen-2-yl-2-pyrrolidin-1-ylpentan-1-one

Chemical Abstracts Service (CAS) registry number
850352-53-3

Molecular information

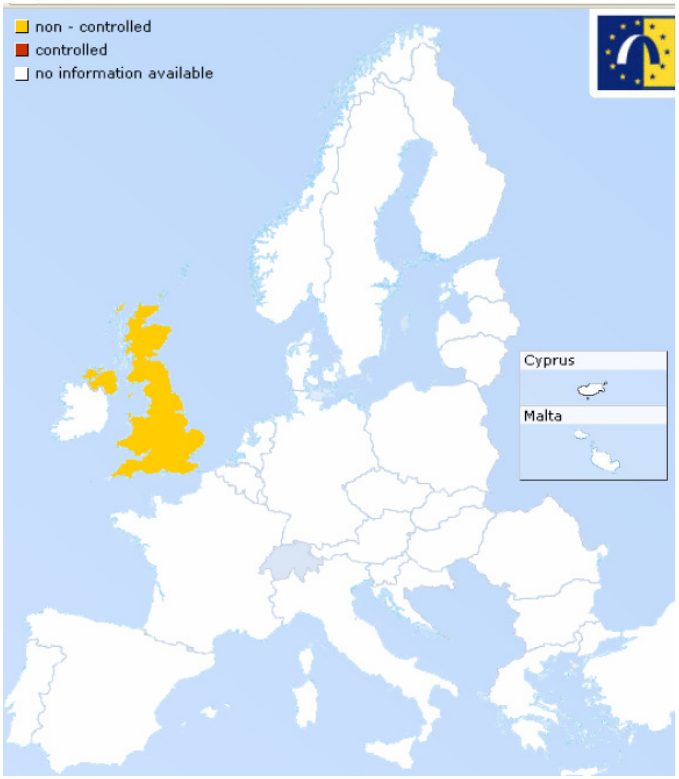
Molecular structure:

File:NVP structure.png



Molecular formula: $C_{19}H_{23}NO$

Molecular weight: 281.39



Identification and analytical profile

.

- Naphyrone Synthesis-1.pdf
  Poster on naphyrone synthesis, provided by the Irish NFP

Synthesis, manufacture and precursors

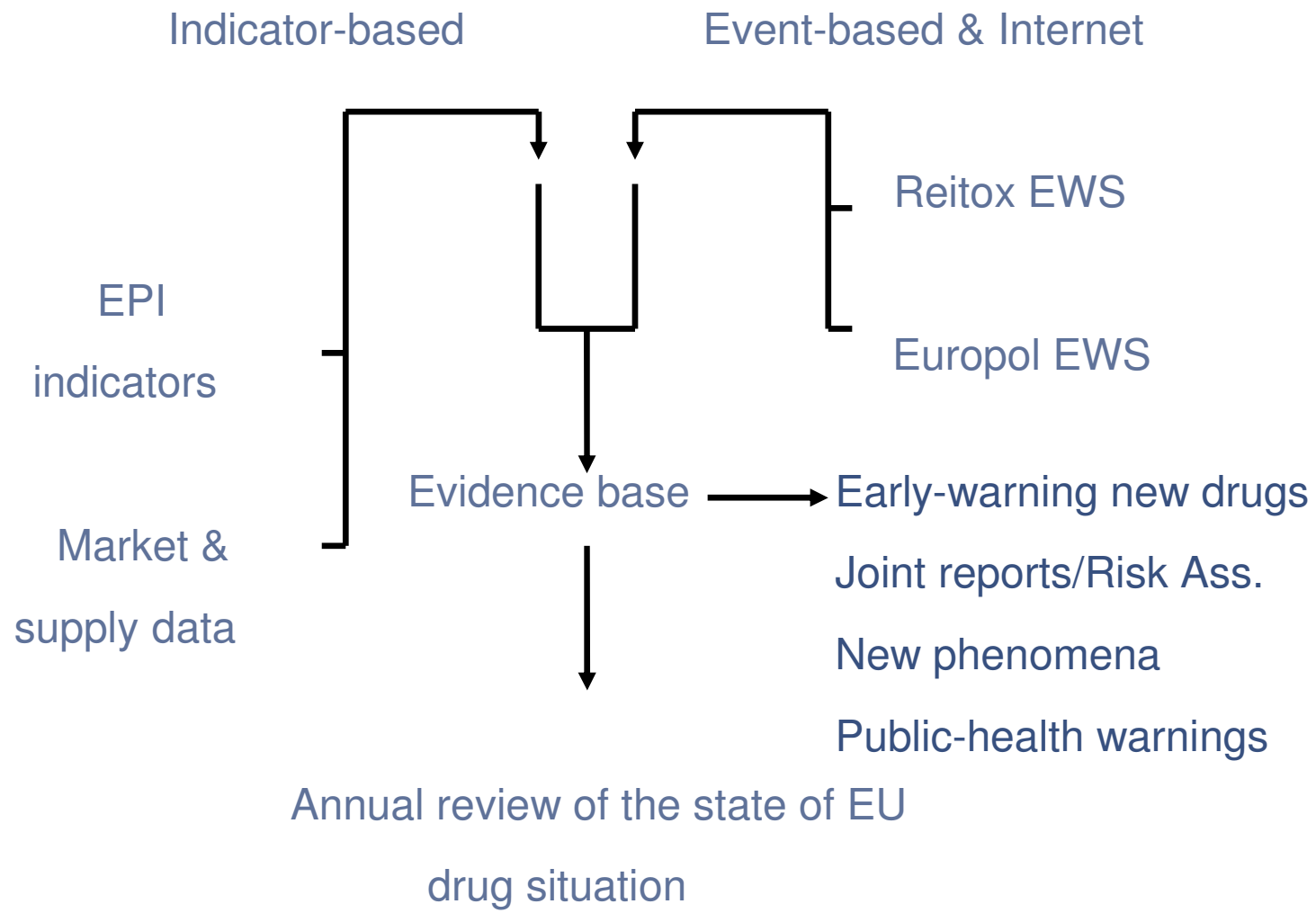
.

Physical description

EWS

Risk assessment

Early-warning system (EWS): sources and outputs

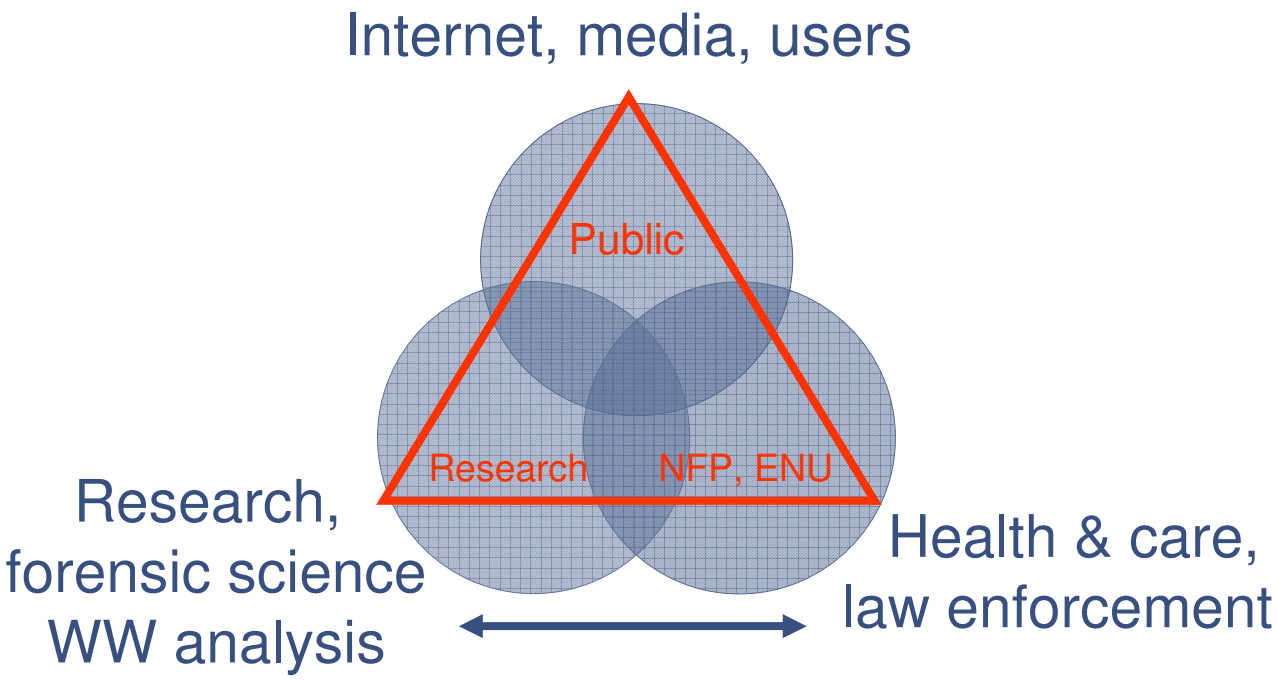


Adapted from R. Kaiser at al., 2005

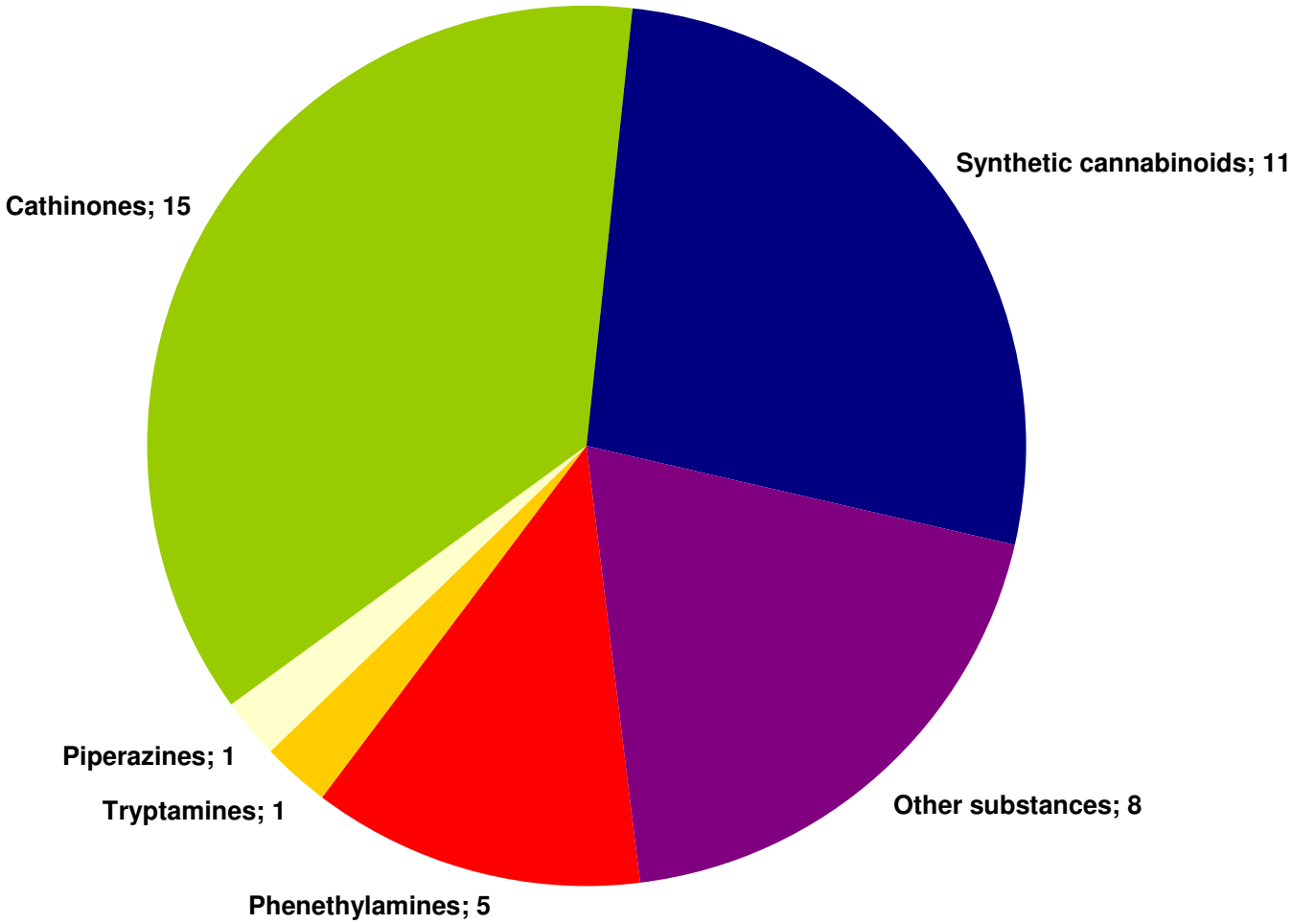
Triangulation of information

EWS

Risk assessment

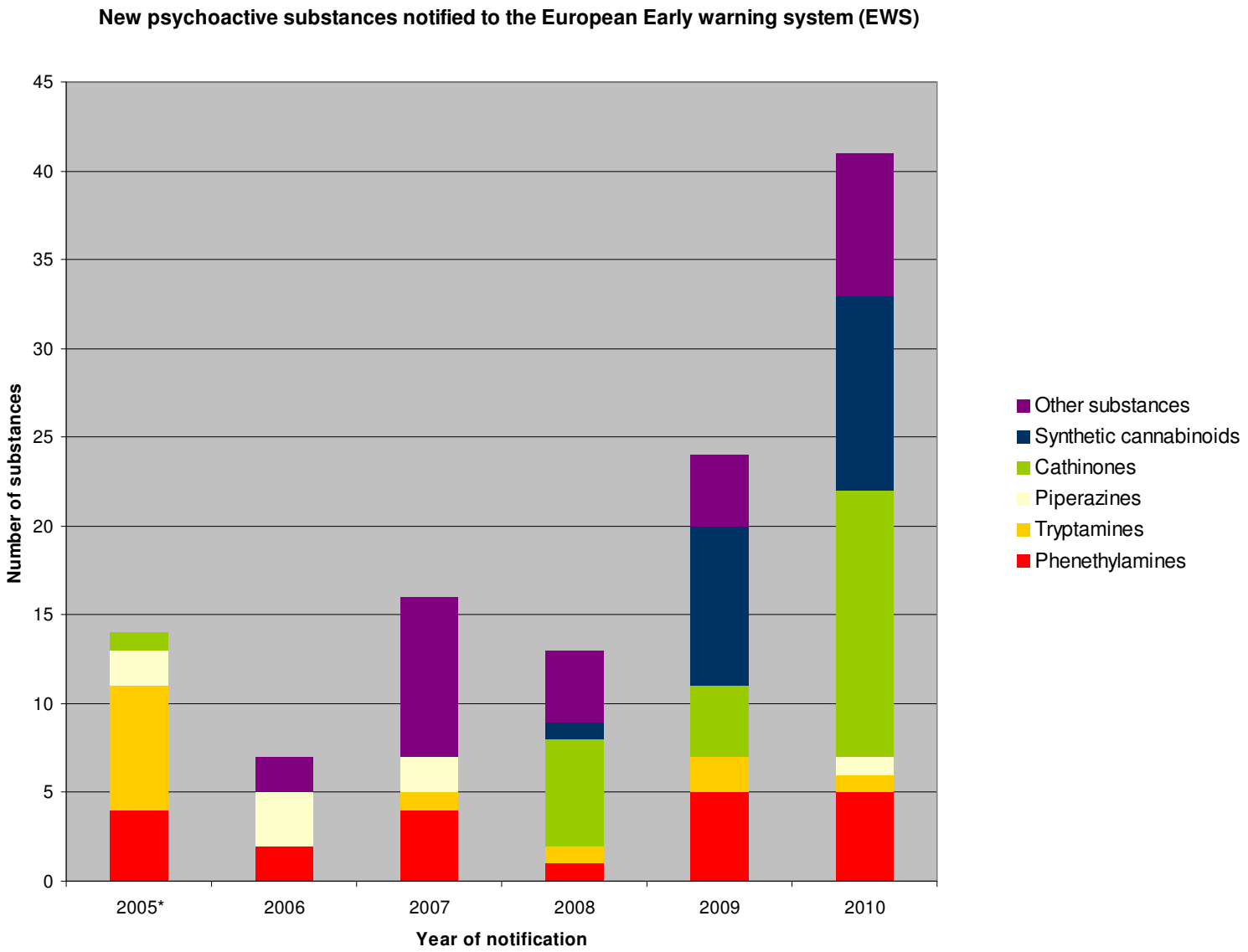


New substances notified by family in 2010



EWS

Risk assessment



…and 2011

EWS

Risk assessment

CRA-13 (naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone) – 11 January 2011 – Germany

4-MeO-PCP (4-methoxyphencyclidine) – 11 January 2011 – Finland

Methylthienylpropamine (N-methyl-1-(thiophen-2-yl)propan-2-amine) – 13 January 2011 – Finland

AM-2201 (1-(5-fluoropentyl)-3-(1-naphthoyl)indole)– 18 January 2011 – Latvia

N,N-dimethylamphetamine (N,N-dimethyl-1-phenylpropan-2-amine) – 2 February 2010 – Bulgaria

JWH-251 (2-(2-methylphenyl)-1-(1-pentyl-1H-indol-3-yl)methanone) – 22 February 2011 – Germany

JWH-018 adamantoyl derivative (1-adamantoyl(1-pentyl-1H-indol-3-yl)methanone) – 22 Feb, Germany

5-IAI (5-Iodo-2-aminoindane) – 1 March 2011, The UK

JWH-182 (naphthoylindole) – 1 March 2011, Denmark

5-IAI (5-iodo-2-aminoindane) – 1 March 2011 – United Kingdom

JWH-250 derivative – 17 March 2011 – Poland

DMMA (3,4-dimethoxymethamphetamine) – 4 April 2011 – France

α-PVP (α-pyrrolidinopentiophenone) – 4 April 2011 – France

EWS

Risk assessment

What has changed?

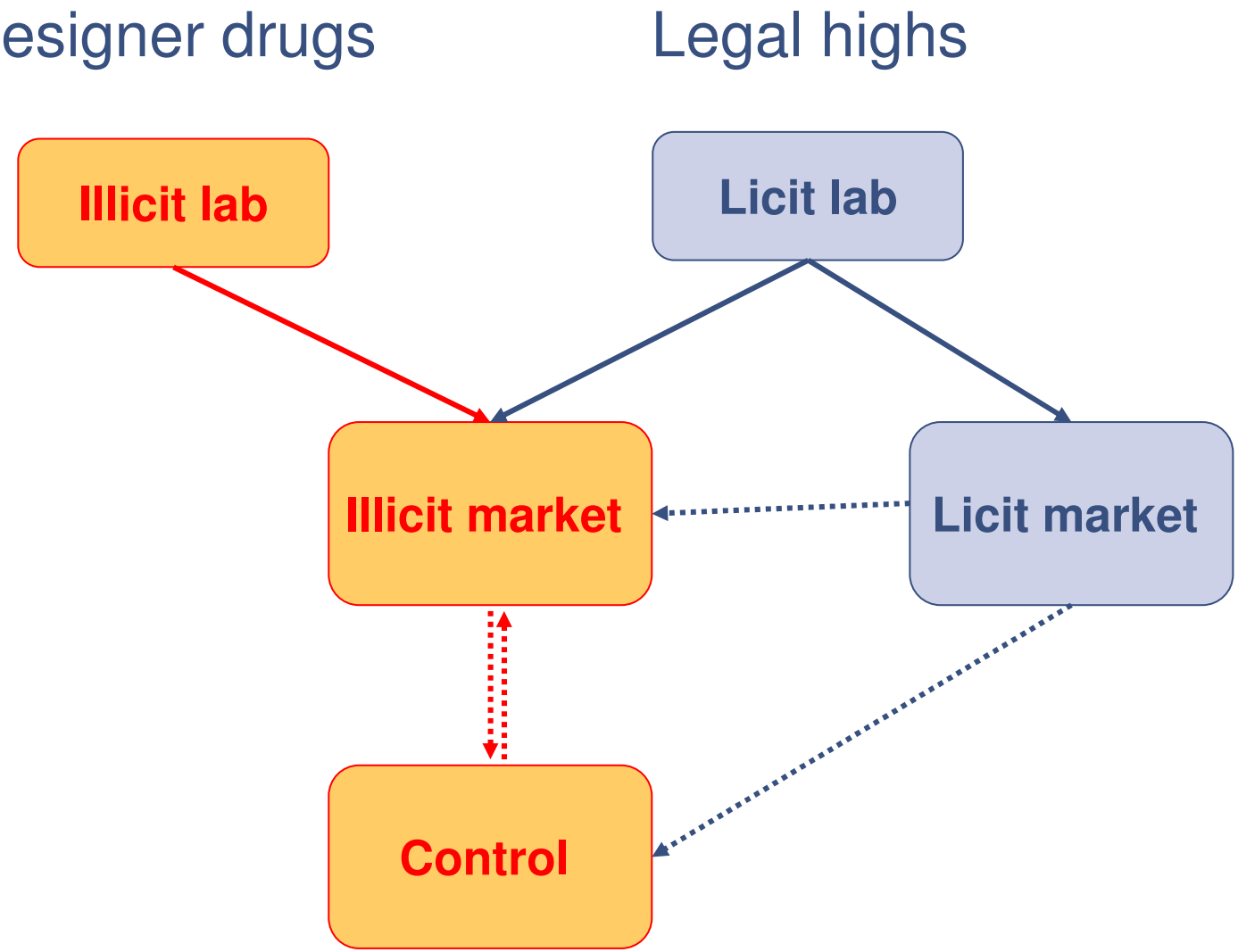
Advances in information technology, Internet as

- Communication tool
- Access to information (medicinal chemistry, patent, etc)
- Market place

Cheap organic synthesis

Entrepreneurship (smart/head/online shops)

Organised crime (?)


Designer drugs
Legal highs
Illicit lab
Licit lab
Illicit market
Licit market
Control

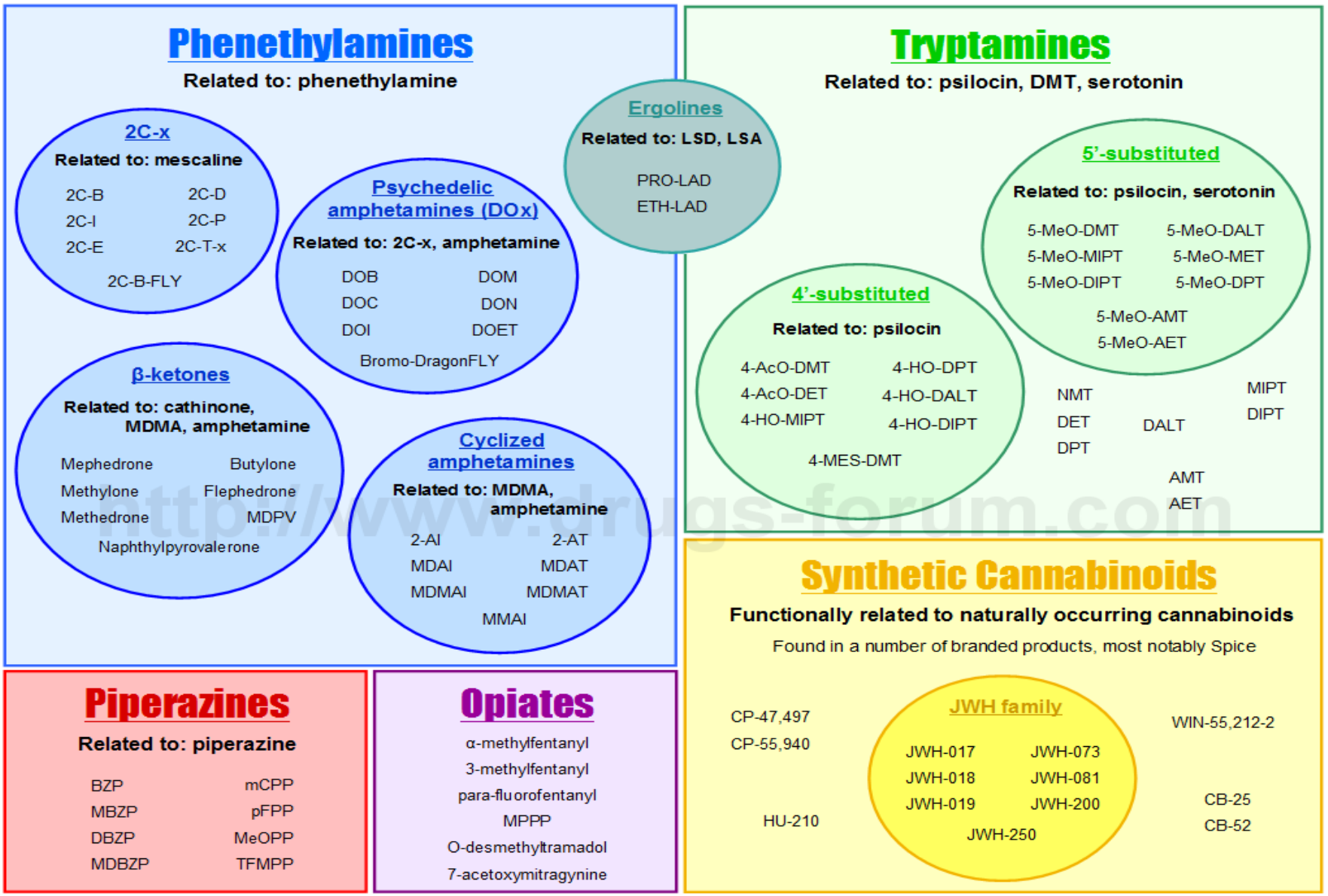
New drugs: a concept in development

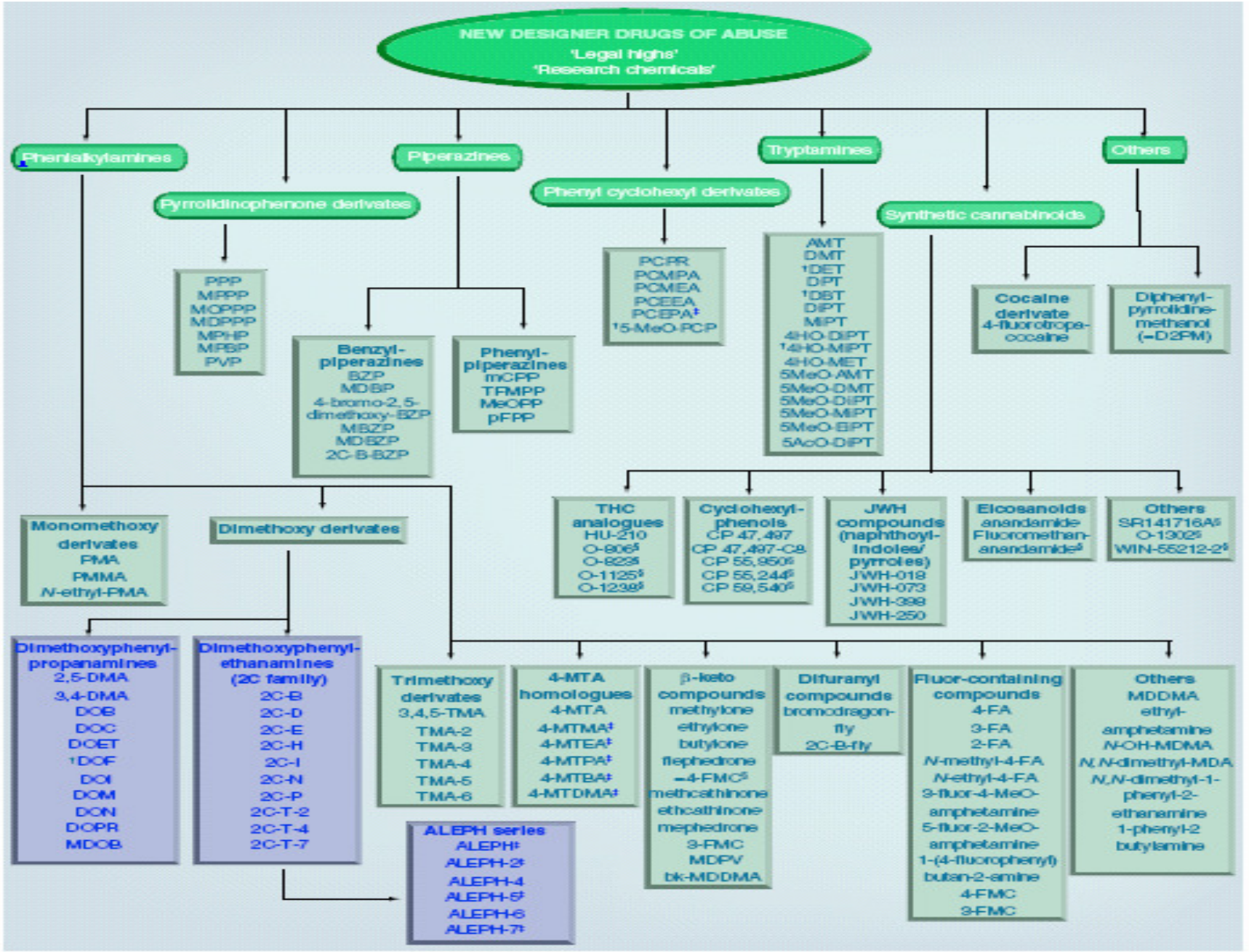
- Designer drugs
- Research chemicals
- Herbal highs
- Legal highs

A multifaceted phenomenon:

- Unregulated psychoactive substances;
- Mimic the effects of known drugs;
- Designed to circumvent control;
- Sold via Internet or specialised shops;
- Advertised with aggressive and sophisticated marketing;
- In some cases intentionally mislabelled;
- Suppliers adapt fast to controls;
- May target specific groups.

New drugs: a concept in development




NEW DESIGNER DRUGS OF ABUSE
'Legal highs'
'Research chemicals'
Phenylalkylamines
Pyrrolidinophenone derivates
Piperazines
Phenyl cyclohexyl derivates
Tryptamines
Synthetic cannabinoids
Others
PPP
MPPP
MOPPP
MDPPP
MPHP
MPBP
PVP
Benzyl-piperazines
BZP
MDBP
4-bromo-2,5-dimethoxy-BZP
MBZP
MDBZP
2C-B-BZP
Phenyl-piperazines
mCPP
TFMPP
MeOPP
pFPP
PCPR
PCMPA
PCMEA
PCEEA
PCEPA‡
¹5-MeO-PCP
AMT
DMT
¹DET
DPT
¹DBT
DIPT
MIPT
4HO-DIPT
¹4HO-MIPT
4HO-MET
5MeO-AMT
5MeO-DMT
5MeO-DIPT
5MeO-MIPT
5MeO-EPT
5AcO-DIPT
Cocaine derivate
4-fluorotropa-cocaine
Diphenyl-pyrrolidine-methanol (=D2PM)
Monomethoxy derivates
PMA
PMMA
N-ethyl-PMA
Dimethoxy derivates
THC analogues
HU-210
O-906§
O-823§
O-1125§
O-1238§
Cyclohexyl-phenols
CP 47,497
CP 47,497-C8
CP 55,950§
CP 55,244§
CP 59,540§
JWH compounds (naphthoyl-indoles/ pyrroles)
JWH-018
JWH-073
JWH-398
JWH-250
Eicosanoids
anandamide
Fluoromethan-anandamide§
Others
SR141716A§
O-1302§
WIN-55212-2§
Dimethoxyphenyl-propanamines
2,5-DMA
3,4-DMA
DOB
DOC
DOET
¹DOF
DOI
DOM
DON
DOPR
MDOB
Dimethoxyphenyl-ethanamines (2C family)
2C-B
2C-D
2C-E
2C-H
2C-I
2C-N
2C-P
2C-T-2
2C-T-4
2C-T-7
ALEPH series
ALEPH‡
ALEPH-2‡
ALEPH-4
ALEPH-5‡
ALEPH-6
ALEPH-7‡
Trimethoxy derivates
3,4,5-TMA
TMA-2
TMA-3
TMA-4
TMA-5
TMA-6
4-MTA homologues
4-MTA
4-MTMA‡
4-MTEA‡
4-MTPA‡
4-MTBA‡
4-MTDMA‡
β-keto compounds
methylone
ethylone
butylone
flephedrone
4-FMC§
methcathinone
ethcathinone
mephedrone
3-FMC
MDPV
bk-MDDMA
Difuranyl compounds
bromodragon-fly
2C-B-fly
Fluor-containing compounds
4-FA
3-FA
2-FA
N-methyl-4-FA
N-ethyl-4-FA
3-fluor-4-MeO-amphetamine
5-fluor-2-MeO-amphetamine
1-(4-fluorophenyl) butan-2-amine
4-FMC
3-FMC
Others
MDDMA
ethyl-amphetamine
N-OH-MDMA
N,N-dimethyl-MDA
N,N-dimethyl-1-phenyl-2-ethanamine
1-phenyl-2 butylamine

Anticipation

EWS

Risk assessment

More derivatives of known drugs

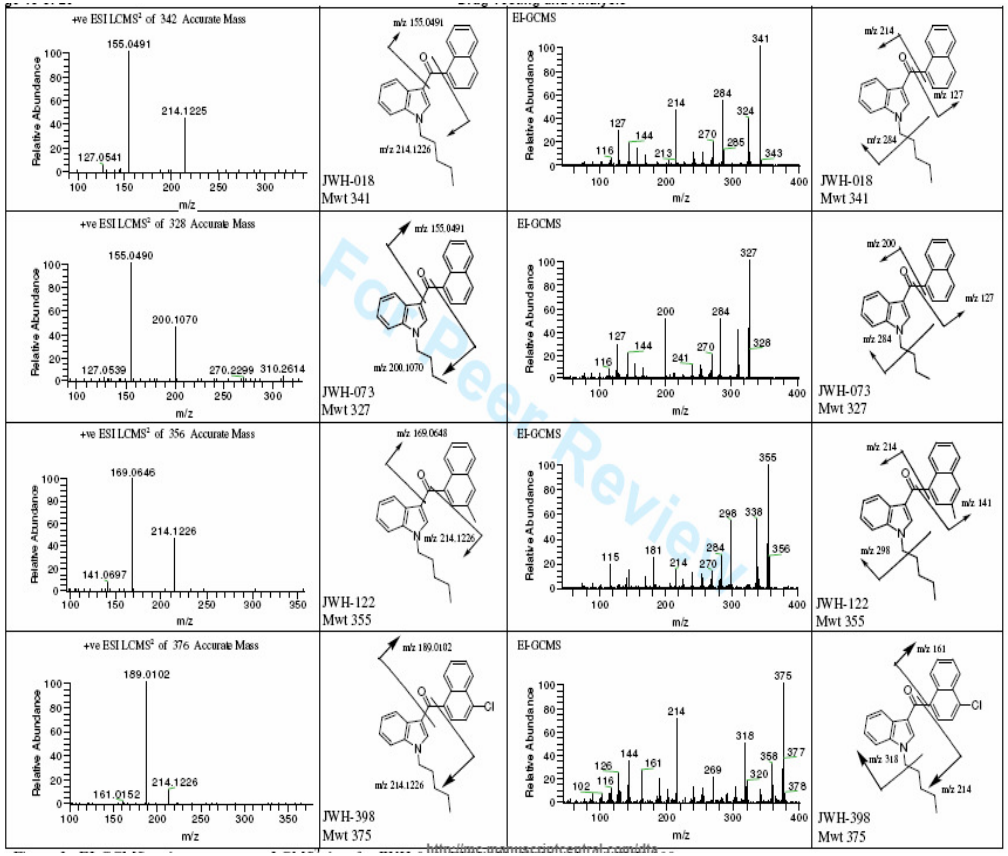
- Synthetic cocaine(s), other stimulants
- PCP & ketamine (latest additions)
- Cannabinoids
- Opioids, sedatives (BDZ?, others)

Designer medicines (medical research)

Metabolites of medicinal products (GHB/GBL)

Medicines

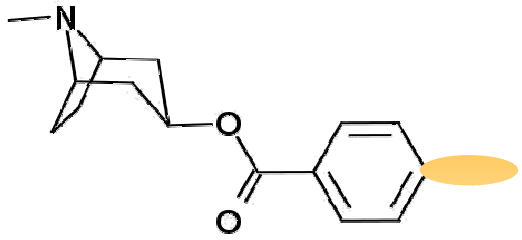
Spice compounds
27 reported to EWS



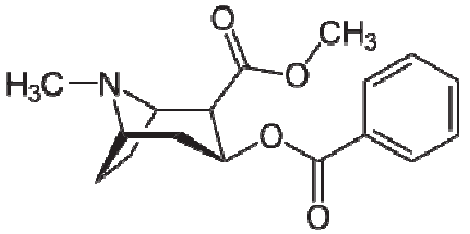
Designer synthetic cocaines

pFBT (fluorotropacocaine, 3-pseudotropyl-4-fluorobenzoate)

- First detection: Finland (2008); identified in head shop products in IE (2010)
- Controlled in Denmark
- Tropane derivative

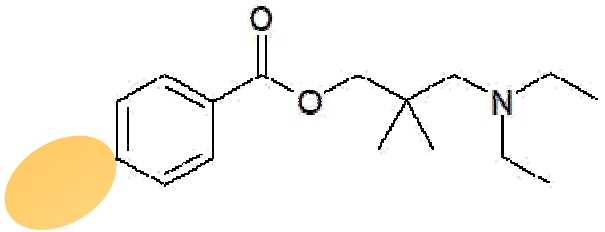


cocaine



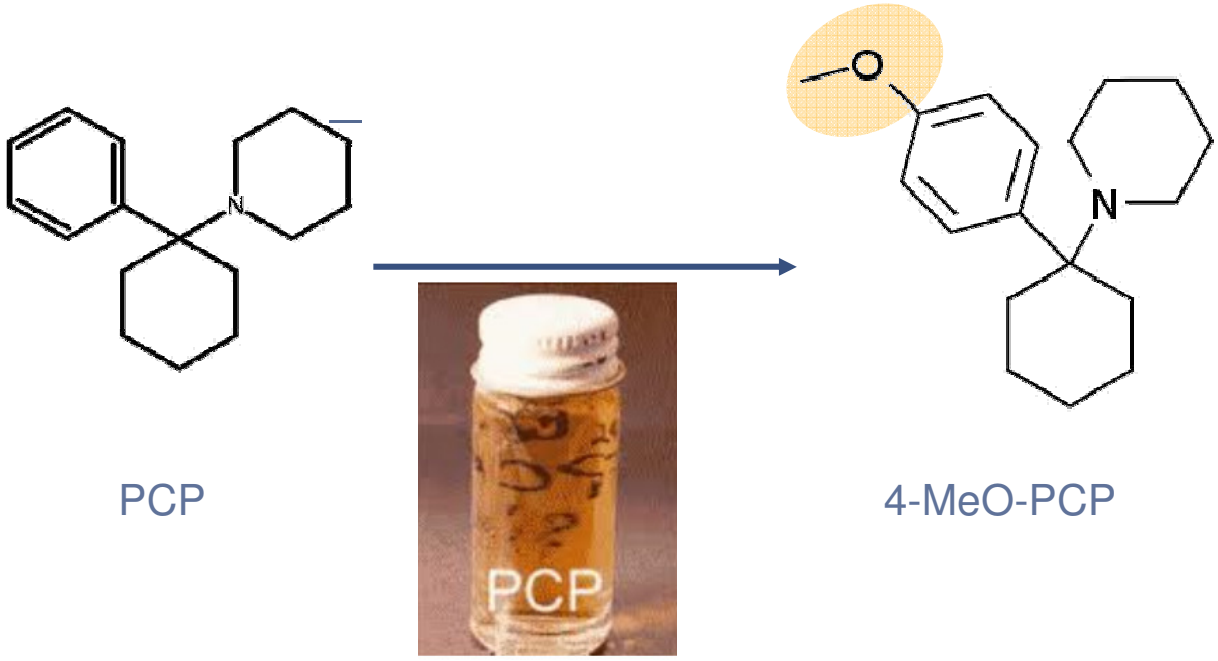
dimethocaine ((3-diethylamino-2,2-dimethylpropyl)-4-aminobenzoate)

- First detection: Ireland (2010); identified in head shop products
- *p*-NH_2 pharmacophore



PCP and 4-MeO-PCP

- Phencyclidine (PCP) is a synthetic dissociative anaesthetic, which is internationally controlled by the 1971 UN Convention on Psychotropic Substances
- The 4-methoxy derivative of PCP (4-MeO-PCP) was notified by Finland in 2011



PCP

4-MeO-PCP

EWS

Risk assessment

Designer medicines – ketamine and methoxetamine

- Ketamine is an anaesthetic and analgesic used in veterinary practice and in human medicine
- It was risk-assessed in 2000
- Methoxetamine is a derivative of ketamine, reported by the UK in 2010

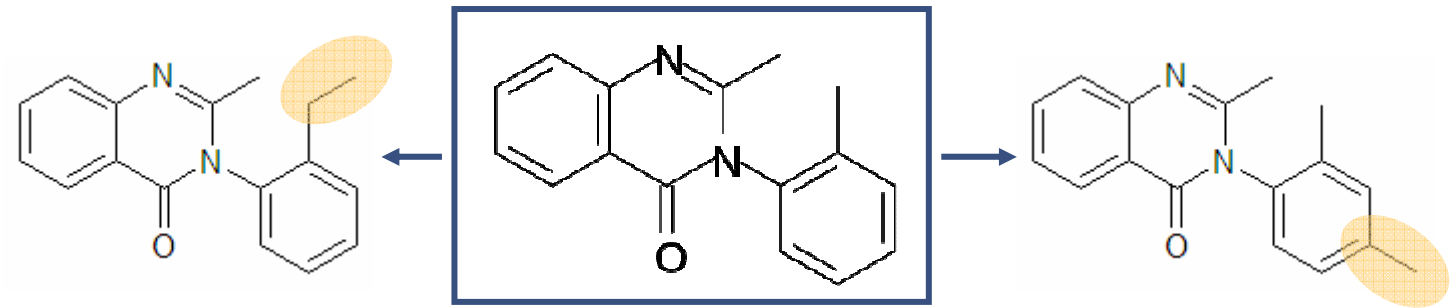
Ketamine

Methoxetamine

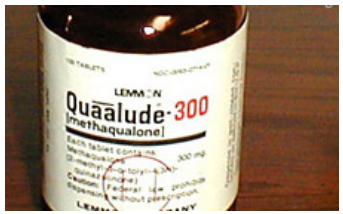
Designer medicines – etaqualone

- Methaqualone was developed in the 1960s and marketed for the treatment of insomnia; it has sedative and hypnotic properties

- Etaqualone was first reported to the EWS by DK in Nov 2009

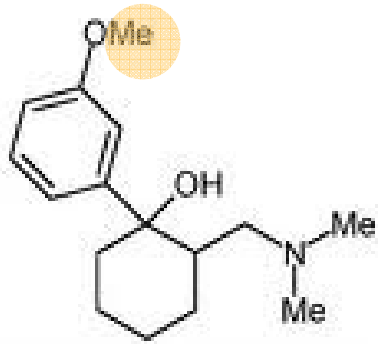


etaqualone methaqualone methylmethaqualone

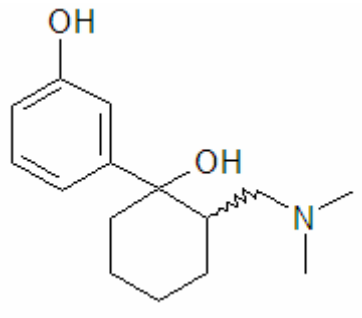


Metabolites of medicines – ODT

- *o*-desmethyltramadol (ODT) is a centrally acting synthetic opioid analgesic
- It is a metabolite of tramadol and a potent μ-opioid agonist
- Reported for the first time by DE, in June 2009

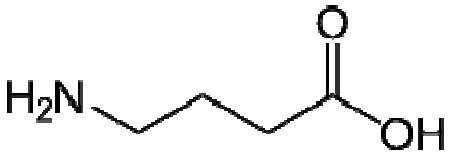


Tramadol

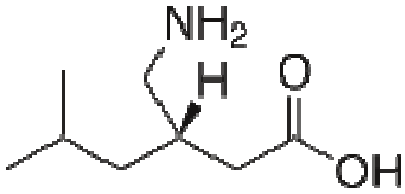


o-desmethyltramadol (ODT)

Misuse of medicines – pregabalin



γ-Aminobutyric acid
(GABA)



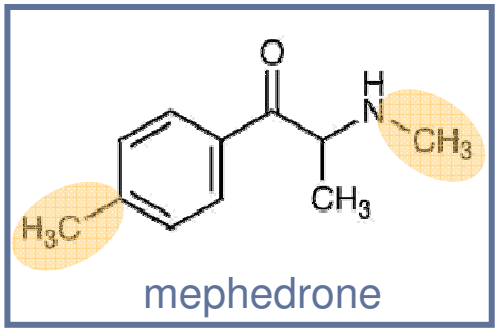
(*S*)-3-(Aminomethyl)-5-methylhexanoic acid
(Pregabalin)

- GABA is a major inhibitory neurotransmitter in mammalian brain - not orally active
- Pregabalin is a derivative of GABA – rapidly absorbed, crosses blood-brain barrier
- BUT: The relationship between Pregabalin and GABA metabolism and GABA receptors is complex

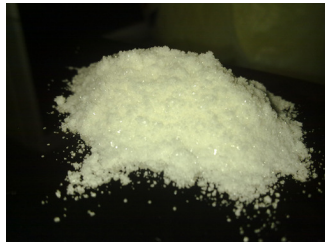
Slide by L A King

4-methylmethcathinone – 'mephedrone'

- It is a synthetic ring-substituted cathinone derivative



mephedrone


white, yellowish powder

- It was first detected in November 2007
- No medical use
- Risk assessment conducted July 2010
- EU wide control (Dec 2010)
- But… already street drug, lack capacity to identify & test, replacements already on the market

Diffusion: why mephedrone?

EWS

Risk assessment

Drivers

Synthetic, easily available
Aggressive marketing
Media
Properties of the substance
- Dose
- Effects
- Toxicity
- ‘Multipurpose’

Changes in the synthetic drugs market

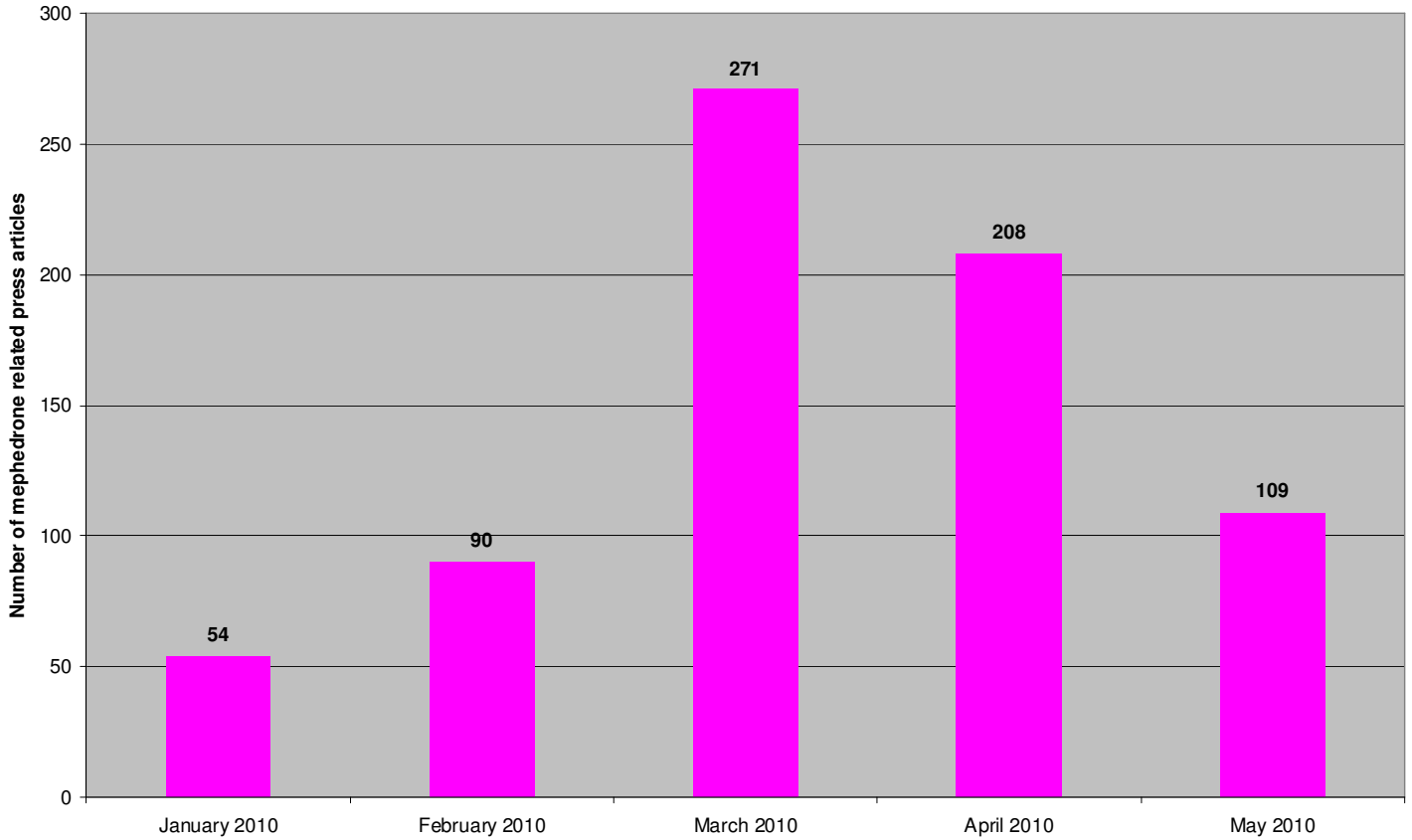
Barriers

Toxicity reports
Control

EWS

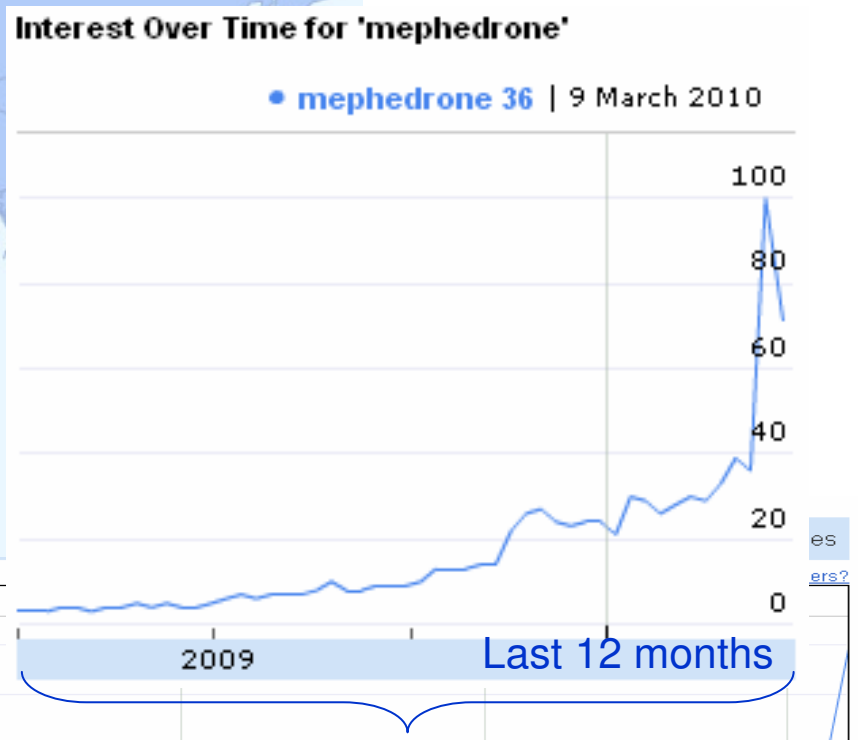
Risk assessment

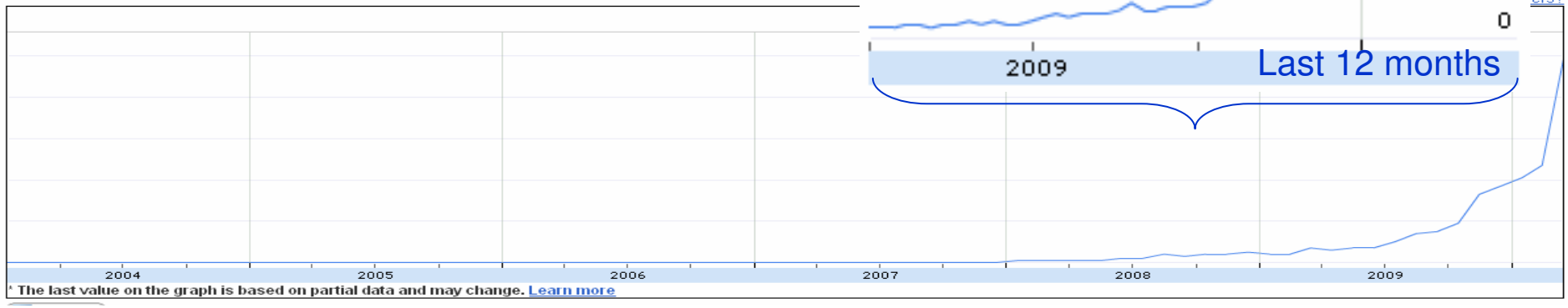
Media coverage



Media coverage likely to be linked with increased awareness among general population and possibly more user interest

Google search



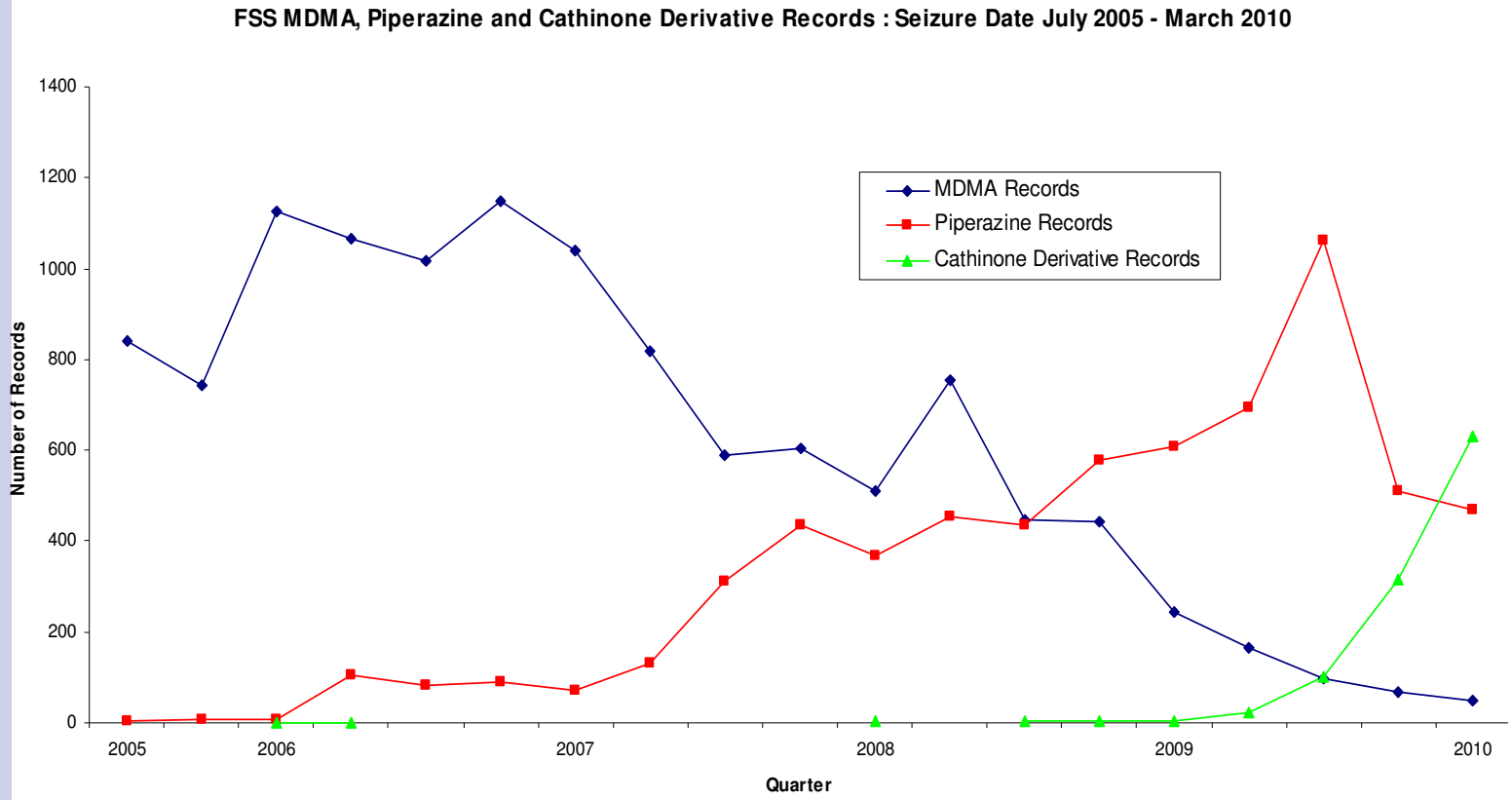


Piperazine, cathinone derivative records

UK Forensic Science Service

EWS

Risk assessment

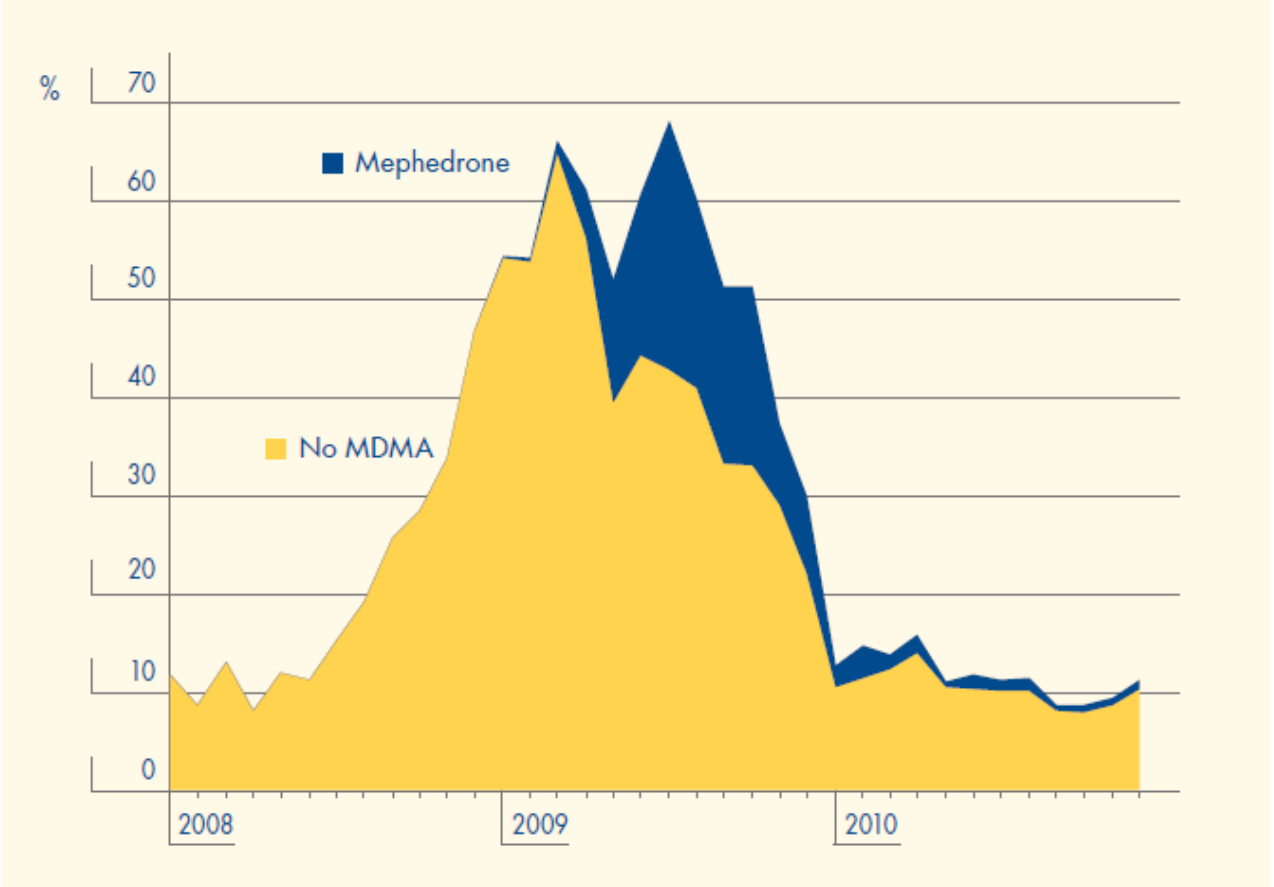


Provided by the UK NFP

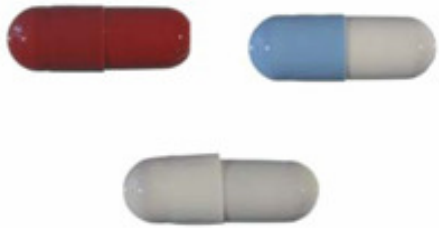
Ecstasy market – DIMS data

EWS

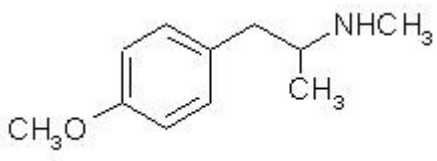
Risk assessment



Brunt T, et al. 2010

	Seizures		Collected samples
Belgium		Netherlands	
Croatia			
Slovakia		United Kingdom	

PMMA (para-methoxymethylamphetamine)



PMMA structurally related to PMA (para-methoxyamphetamine) and methamphetamine. PMMA, especially when associated with PMA in 'ecstasy' like tablets, appears to be associated with a higher risk of acute effects including adverse reactions and overdose.

Both PMA and PMMA are known to have considerable toxicity and to have been responsible for fatal overdoses in the past. PMA has been listed in Schedule I of the 1971 UN Convention on Psychotropic Substances since 1986, whereas PMMA is controlled at EU level Since 2002 following the EMCDDA risk assessment of 2001.

Alert send on 29 October 2010, by the Norwegian NFP to the EWS – PMMA detected in blood samples from 6 overdose death cases (July – September 2010)

Perspectives

- Very rapidly changing market place
- (Lack of) capacity to test and identify substances
- Increasing convergence with the illicit drug market
- Very little data on risks
- Legal measures (difficult to formulate?)
- But some substances are clearly damaging to health
- Expect… more stimulants, drugs modelled on medicinal products and sedatives

EWS (Internet)

Risk assessment

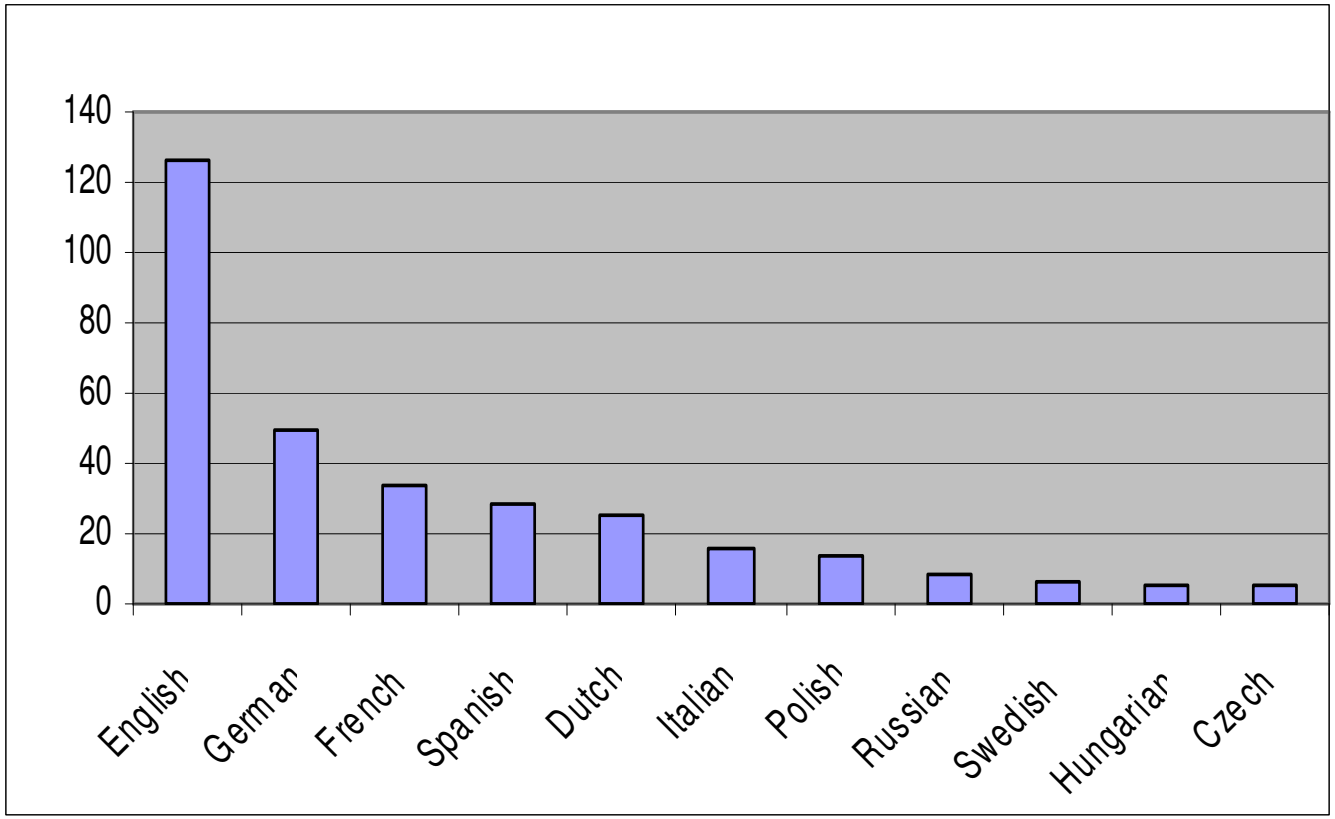
EMCDDA snapshot 2010 (‘legal highs’)

- 170 online shops identified – increase from earlier
- Interface language: EN only 40%, multilanguage (other language plus EN) 35%, Non-EN 25%.
- ‘Legal highs’ offered at 136 sites
- Hallucinogenic (‘magic’) mushrooms offered at 64 sites
- GHB (alternative) or GBL offered at 9 sites
- Number of sites with different kinds of ‘legal highs’: Spice 21 (only 14 had stock); Salvia 57; Kratom 55; ‘Magic’ mushrooms (no mention of psilocybin); grow kits 31 ; ‘Magic’ mushrooms (or truffles) ready for consumption 32 ; ‘Magic’ mushrooms capsules 4

EMCDDA snapshot results 2010 -'legal highs' – Interface language

EWS (Internet)

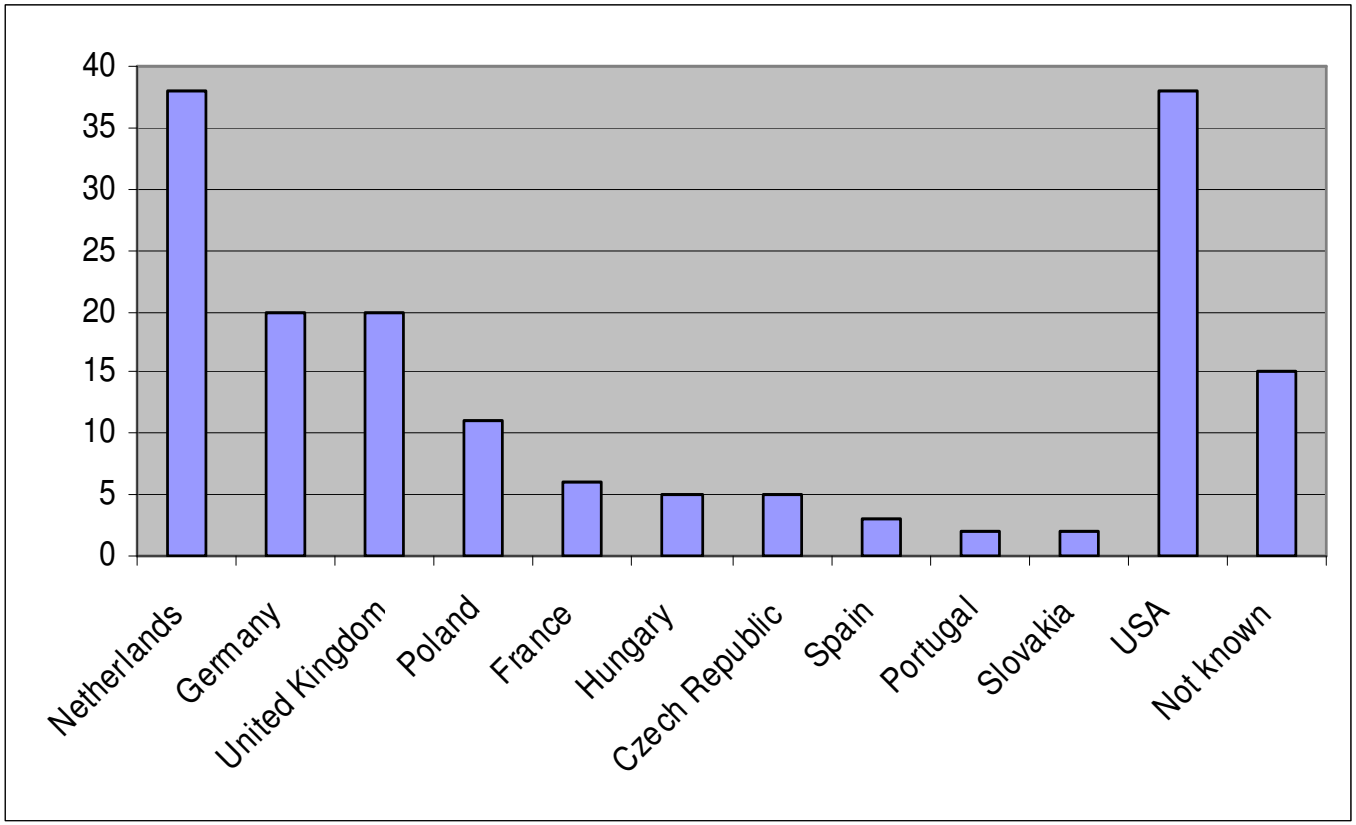
Risk assessment



EMCDDA snapshot results 2010 -'legal highs' – 'Country of origin'

EWS (Internet)

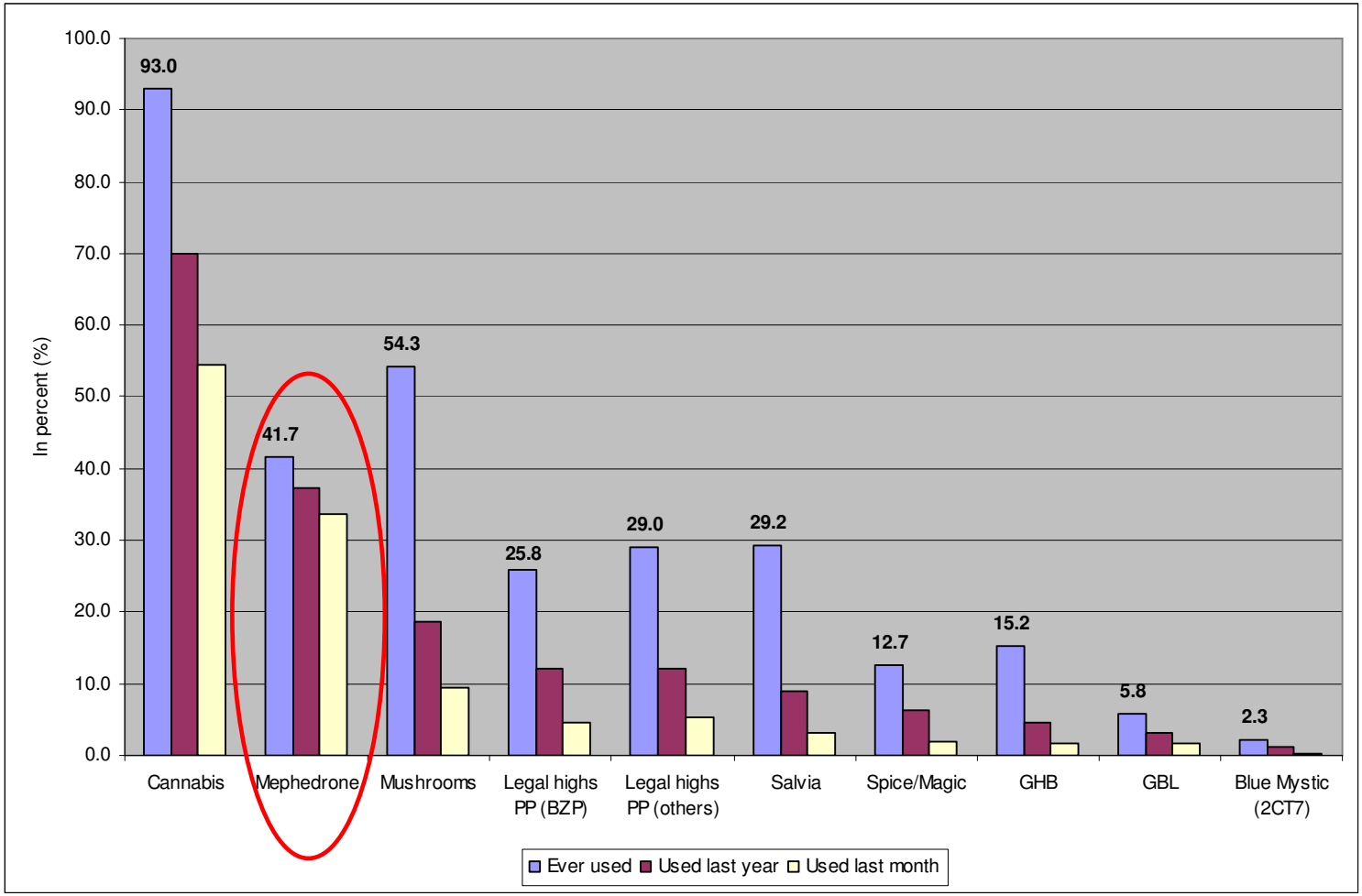
Risk assessment



Prevalence of ‘legal highs’

- Mixmag survey 2010 found that 54% of respondents had ever tried hallucinogenic mushrooms and 41% had ever tried mephedrone
- Mixmag survey 2011 found that 61% of respondents had ever tried mephedrone
- A 2008 Polish study amongst 18-year-old students found that 3.5% had ever tried ‘legal highs’
- A 2009 Polish study found 10 % of the respondents in the 15–24 age group, reported ever having used ‘legal highs’
- Same survey found 6 % between 15 and 75 years of age had ever tried ‘legal highs’ and 5 % had tried within the last year

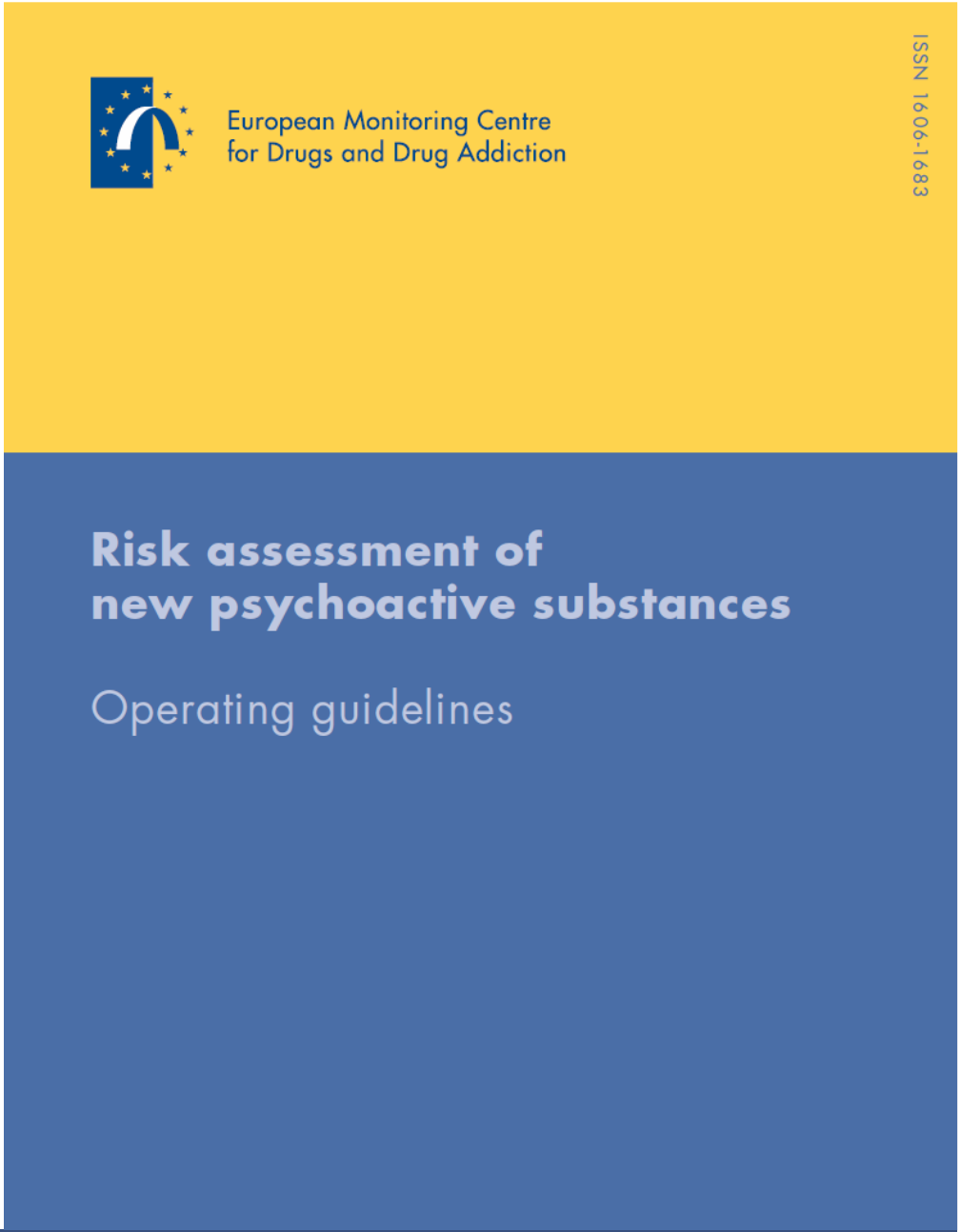
Mixmag survey (online, 2009/10)



Outline

- Factors to be considered
- General 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



General considerations for risk assessment

- Dual definition of risk
  - ‘risk’: probability that some harm may occur
  - ‘hazard’: degree of seriousness of such a harm
- Prevalence of use
  - evidence that the substance is being (or is likely to be) used so as to constitute a public health and social threat
- Potential benefits
  - Substances with therapeutic value may be exempted
- Risks of a substance, independently of its legal status
- Scientific evidence in relation to better-known substances
- Quality of data
- Weighing the issues of reliability and relevance separately

Conceptual framework for risk assessment (1)

Source of hazard

Sources of hazard emanating from:

- intrinsic properties of the substance (pharmacology and toxicology)
- measures of social control (regulatory policies and informal norms)
- modalities of substance use (patterns, context of use)
- individual characteristics of users (age, gender, genetics, personality)

Conceptual framework for risk assessment (2)

Hazardous effects of a substance

(a) On the user:

- biological (toxicity, dependence)
- psychological (functional impairment, effects on personality)
- behavioural (neglect of social roles, violence, etc.)

(b) On the social environment:

- family — micro level (disruption, neglect, violence)
- neighbourhood and community — meso level (public order and safety)
- society at large — macro level (economy, public health and judicial systems)

Key variables

- Dose and frequency of use
- Short-term and especially long-term effects
- Interactions with other substances (including alcohol and medicines)
- Individual characteristics (e.g. genetic susceptibility, presence of interacting risk factors)
- Characteristics of the social and cultural environment
- Involvement of organised crime

Types of evidence

- Laboratory evidence, either *in vitro* or *in vivo* (mainly animals)
- Evidence of effects on humans (biological and psychological)
- Epidemiological evidence
- Sociological evidence
- Criminological evidence

(b) Health risks (1)

Elements for assessing individual health risks

- Acute toxicity, including safety profile and information on poisonings
- Chronic toxicity, including functional brain damage, reproductive toxicity, genotoxicity and carcinogenic potential
- Dependence potential (physical and psychological)
- Psycho-social dysfunction
- Similarities and differences to other reference substances

(b) Health risks (2)

Elements for assessing public health risks

- Extent, frequency and patterns of use
- Availability and quality of the new psychoactive substance on the market (purity, adulterants, etc.)
- Availability of information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects
- Characteristics and behaviour of users (including risk factors, vulnerability, etc.)
- Nature and extent of health consequences (e.g. acute emergencies, poisonings, road traffic accidents)
- Long-term consequences of use (e.g. irreversible toxicity leading to deterioration of health at later stages of life)
- Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks (e.g. continuous dancing in hot environments, other substances used)

(c) Social risks

Elements for assessing social risks

- Individual social risks (e.g. impact on education or career, problems with personal relationships)
- Possible effects on direct social environment (e.g. neglect of family, violence)
- Possible effects on society as a whole (public order and safety, acquisitive crime)
- Economic costs (demands on health care)
- Possible effects related to cultural context, for example marginalisation
- Possible appeal of the new psychoactive substance to specific population groups within the general population

(d) Involvement of organised crime

Elements for assessing the involvement of organised crime

- Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain
- Impact on the production, trafficking and distribution of other substances, including existing as well as new psychoactive substances
- Evidence that the same groups or people are involved in different kinds of crime
- Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)
- Evidence of money-laundering practices, or impact of organised crime on other socio-economical factors in society
- Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)
- Use of violence between or within criminal groups
- Evidence of strategies to prevent prosecution, for example through corruption or intimidation

Semi-quantitative assessment procedure

- The experts send their sheets with the scores by e-mail to the Chair of the Scientific Committee, who makes an overall summary of the judgement sheets. This will contain:

  i) a copy of all **judgement sheets**

  ii) the **mean value of the individual RLs** given for the 19 subgroups, arranged per subgroup

  iii) the **average risk (AR) value of the five domains**

  iv) the **list with subgroups** on which there is **agreement/consensus** (similar score by all experts; variation in score ≤ 1)

  v) the **list with subgroups** on which there is apparent **disagreement** (a range of different RLs given for a subgroup in which the variation > 1)

  vi) the **list of all remarks** arranged per subgroup.

- The **overall summary is distributed** to all members.

Semi-quantitative assessment procedure

Delphi approach

- On the day of decision, the Chair discusses with all members of the Scientific Committee points v) and vi) of the overall summary.
- Each expert is allowed to change his/her numerical score on the second judgement sheet.
- The Chair produces a final assessment report that contains:
  - a copy of all second judgement sheets
  - the mean value of the (revised) individual RLs for the 19 subgroups, arranged per subgroup
  - the average risk (AR) value of the five domains
- The EMCDDA's Scientific Committee makes a final judgement on the risks of the new psychoactive substance taking into account the final assessment report and formulates a **conclusion**.

GHB/GBL: an emerging trend

Contacts

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