

## **Designer Drugs / Research Chemicals / Legal Highs - A survey of recent seizures and an attempt to a more effective handling from a Swiss perspective**

**Michael Bovens, Markus Schläpfer**

Forensic Science Institute Zürich, Zeughausstrasse 11, Postfach, CH-8021 Zürich, Switzerland

---

**Key words:** Designer Drug, Research Chemical, Analogues, Generic, Legal High, Drug Law

### **Abstract**

Since the first seizure of synthetic cannabinoids (“Spice” in 2007) on the illegal drug market in Switzerland, there has been an enormous increase of substances of different chemical classes. The diversity of different cannabinoids (JWH-, WIN-, CP- and HU-substances) increased greatly and different amphetamines (e.g. 4-fluoroamphetamine), cathinone derivatives (e.g. mephedrone, methylon, fluoromethcathinone) piperazines (e.g. m-CPP, o-CPP) tryptamines and more recently alkyl amines (e.g. geranamine), benzofuranes (e.g. 5-APB) and indanes (e.g. 5-IAI) appeared both on the market and as seizures.

Little is known about the toxicological and pharmacological effects of those single substances let alone of interactions in mixtures of such substances. Frequently seized products consist of mixtures e.g. stimulants combined with local anaesthetics and hypnotics. Many products with very professional appearance (fancy wrappings with faked ingredient lists and even holographic quality labels) mislead consumers and pretend quality controlled production.

In Switzerland the legal status of such substances or products is poorly defined as according to the narcotics act each single substance has to be listed individually and the process of listing new substances is very slow. Substances, even though they are pharmacologically active are not considered medicals unless they were used therapeutically at any time or place. As the import and possession of a 30 day supply even of unapproved medicals is legal, there is virtually practically no regulation at all.

As an attempt to overcome these problems the implementation of a new “provisional register” into the narcotics regulation with the aim to be able to quickly react onto new drug trends is planned and is presented. In analogy to several European and Non-European countries the introduction of a more extensive “generic clause” or an “analogues act” is currently under judicial verification and is an unquestioned need to be defined and introduced in the near future.

### **1. Introduction**

Not a day goes by without seizures of suspicious materials (e.g. powders, tablets, liquids) at the customs. These materials have to be analyzed in forensic drug laboratories to investigate their true identity. So called 'legal highs', research chemicals or designer drugs are mainly traded on the internet and delivered by mail. Street trading like with the traditional drugs heroin and cocaine is uncommon in Switzerland.

The identification of such substances, as single compounds or in mixtures is challenging and reference materials are difficult to get. Ironically some of the reference materials used by forensic laboratories frequently originate from the same companies, which produce for the recreational drug market. Interestingly the time frame between the announcement of a new research chemical from a producer – there are dozens of them worldwide [1] – and the appea-

rance on the designer drug market (apparent by seizures at the customs) is only a few days or weeks! This clearly demonstrates the speed and potential for “big business” in this area.

It is self-evident that these designer drugs are consumed and will appear unmetabolized or metabolized in blood, urine, saliva and hair and must be identified in these matrices. As such they will also challenge toxicologists and medical practitioner concerning the driving ability.

Beside the producers of designer drugs and the selling companies we encounter an increasing activity in forums on the internet. Not only consumers exchange their experiences after consumption or ask questions on doses and effects, but also chemists and pharmacologists discuss potential or expected effects and try to develop new designer drugs further.

Two goals are basically pursued: Firstly the drug law should be bypassed by producing so called 'legal highs'. Secondly new substances with comparable or even better effects in terms of lower doses and less side effects should be created. The driving force behind all these activities is of course the money on this remunerative market.

Most national drug laws can not follow this fast development of designer drugs and are still laid-out for the former 'old' and 'naturally' occurring drugs. To take account of the fact, that the variety of designer drugs changes rapidly, drug laws have to be adapted. A listing based on single compounds is no longer adequate as it is too slow and only reactive. A general listing of problematic **substance classes** by a **generic clause** could be an effective tool to meet this problem and would be a **proactive** step to prevent production and trade of new designer drugs of at least those substance classes listed.

The most problematic substance classes encountered in Switzerland according to our ongoing survey in decreasing order of appearance are:

Phenethylamines > Synthetic Cannabinoids > Piperazines > Tryptamines > Synthetic Opioids >> Ergolines

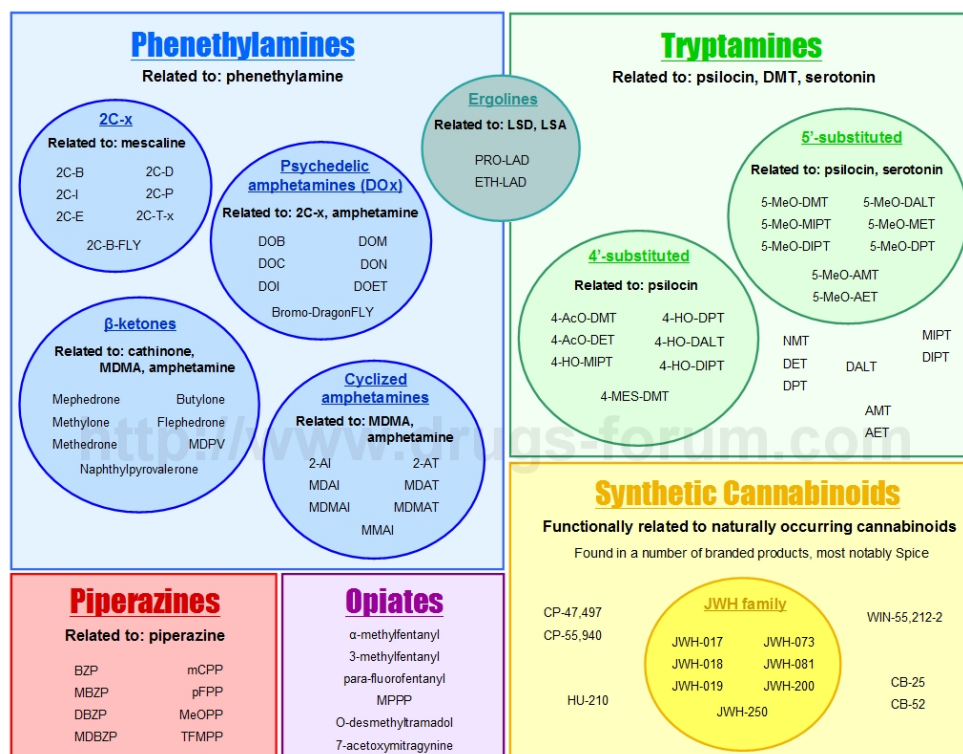


Fig. 1. Overview of the most frequently encountered substance classes of designer drugs [1].

Among the phenethylamines the subclass of the cathinones (β-ketones) developed fastest, followed by the 2C-series and the amphetamines.

## 2. Material and Methods

### 2.1. Material

All the designer drugs mentioned here were either ordered as single substances directly via internet [2] or were seized by the customs and received for forensic analysis (usual casework). The variety is far bigger than can be mentioned here. The listed examples should give a small insight into the development within the mentioned problematic substance classes (Fig. 1).

### 2.2. Analytical techniques

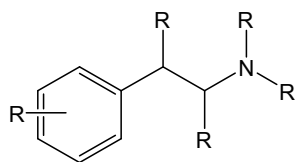
The analytical technique of choice to identify designer drugs is GC-MS after a basic workup or after a derivatization step (e.g. silylation, acetylation, trifluoroacetylation...). Also MS<sup>n</sup> techniques can be helpful. An additional confirmation of pure (or at least purified) substances by NMR is always recommendable if reference material is lacking. The presented designer drugs are at least identified by GC-MS after derivatization with TMS.

### 2.3. GC-MS parameters

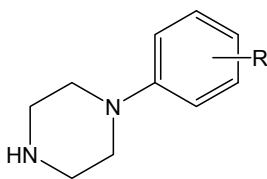
Column: HP-5-MS, 30 m; 0.25 mm, 0.25 μm; Temperature: 80°C – 320°C mit 15°C/min, 4 min 320°C; Gas: Helium 5.0, const flow 1.1 ml/min; Injector: SSL 280°C; Split ratio: 25; Transfer line 310°C; Source: 200°C; Range: TIC: 30 – 650 amu; Solvent delay: 2 min

## 3. Results and Discussion

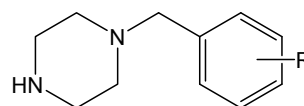
In the following derivatives of the classes and subclasses of phenethylamines, piperazines and synthetic cannabinoids are presented. Potential substitution sites are indicated with “R”. Examples of such products appeared already on the market but they are single puzzle-pieces of an only partly known bigger picture.



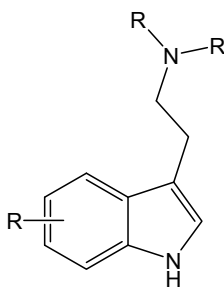
Phenethylamines



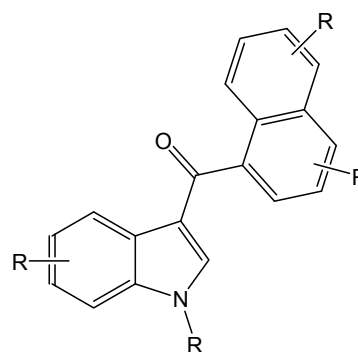
Phenyl-Piperazines



Benzyl-Piperazines



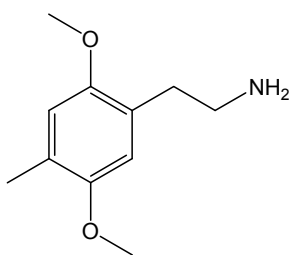
Tryptamines



Synthetic Cannabinoids (JWH-type)

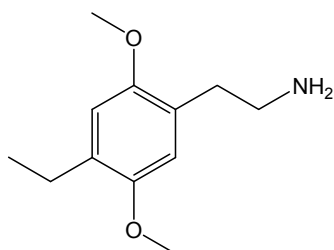
### 3.1. Class of Phenethylamines (2C-serie)

Four 2C-compounds are currently listed in the Swiss drug law (2C-B, 2C-I, 2C-T-2 and 2C-T-7). After appearance of a new derivative 2C-D (1-(2,5-dimethoxy-4-methylphenyl)-2-aminoethane (**1**) on the homepage of a producer of fine chemicals (known to the author) it took only a few weeks and this compound appeared pelletized and sold via internet as a designer drug, packed in small aluminium cans, containing 2 tablets each. The etiquette on the lid declares 'Not for human consumption'. However, on the backside of the can a short description explains the preferred way of consumption! In the meantime six other similarly packaged tablet products with different logos containing all different designer drugs appeared on the internet-market and in our laboratory!

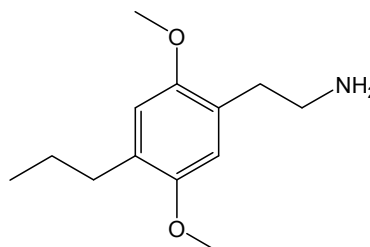


**(1)**  
2C-D  
2,5-Dimethoxy-4-methyl-phenethylamine

Further derivatives like the ethyl- and propyl-analogue 2C-E (**2**) and 2C-P (**3**) are also already available.



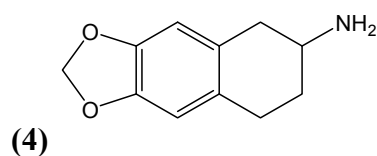
**(2)**  
2C-E  
2,5-Dimethoxy-4-ethyl-phenethylamine



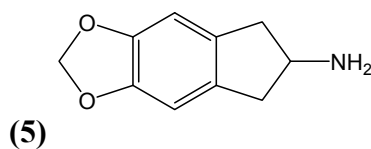
**(3)**  
2C-P  
2,5-Dimethoxy-4-propyl-phenethylamine

### 3.2. Class of Phenethylamines ('Amphetamines')

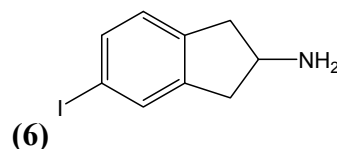
The variation in this subclass is so wide that the term 'amphetamines' is chemically not correct anymore. For example MDAT (6,7-methylenedioxy-2-aminotetralin (**4**) a derivative of MDMA where the amphetamine structure is changed by a ring closure. MDAT is considered likely to be a non-neurotoxic, putative entactogen [3].



MDAT  
6,7-methylenedioxy-2-aminotetralin



MDAI  
5,6-methylenedioxy-2-aminoindane

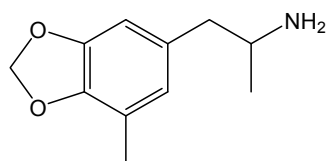


5-IAI  
5-iodo-2-aminoindane

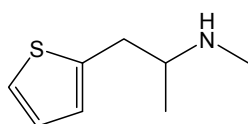
Instead of the 6-ring closure a 5-ring closure has been observed as well, leading to compounds known as aminoindanes like MDAI (5,6-methylenedioxy-2-aminoindane **(5)**). The replacement of the methylenedioxy-group with iodine leads to 5-IAI (5-iodo-2-aminoindane **(6)**).

With 5-Methyl-MDA **(7)**, a first substance appeared, which in addition to the 3,4-methylenedioxy-group, has a methyl-group at the phenyl ring. Even the substitution of the phenyl-group with a thiophene-group resulting in a molecule called methiopropamine **(8)** has been seized by the customs. Methiopropamine is reported to be also a stimulant.[4].

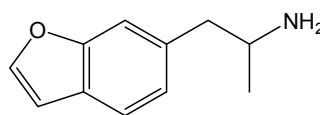
Of most of these new substances a clear pharmacological explanation is not yet known and fully understood. Last but not least BenzoFury (6-APB, 6-(2-aminopropyl)benzofuran) **(9)** as well as its isomer 5-APB **(10)** are on the market and seized by the customs).



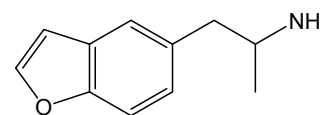
5-Methyl-MDA  
5-Methyl-3,4-methylenedioxy-amphetamine



Methiopropamine  
1-(Thiophen-2-yl)-2-methylamino-propane



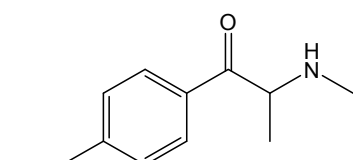
6-APB  
6-(2-Aminopropyl)benzofuran



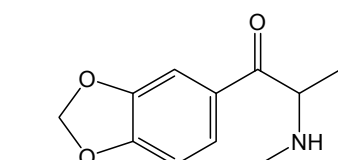
5-APB  
5-(2-Aminopropyl)benzofuran

### 3.3. Class of Phenethylamines (Cathinones)

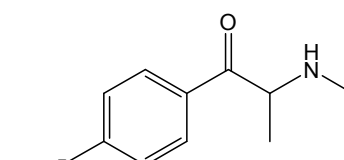
Synthetic cathinones are related to the parent compound cathinone, one of the psychoactive principals in khat (*Catha edulis*). Cathinone derivatives are the  $\beta$ -keto analogues of the corresponding phenethylamines. Since the mid-2000s, unregulated ring-substituted cathinone derivatives appeared on the European recreational drugs market. The best-selling cathinones in the period up to 2010 appeared to be mephedrone **(11)** and methylone **(12)** [5].



Mephedrone  
4-Methylmethcathinone



Methylone  
3,4-Methylenedioxy-N-methylcathinone



Flephedrone  
4-Fluoromethcathinone

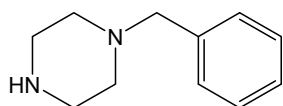
The development within the cathinone family is – from our point of view – more or less comparable with the amphetamines. 3,4-methylenedioxy compounds, as well as halogenated and alkylated derivatives already appeared.

### 3.4. Class of Piperazines

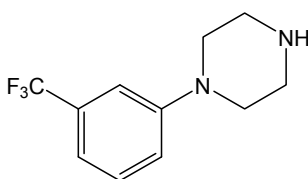
After the shortage of PMK on the illegal market of precursors since around 2007 the number of seizures of MDMA containing XTC tablets decreased significantly. MDMA seemed to have been replaced first by BZP (**14**) and TFMPP (**15**) – often these two piperazines appeared in combination as this mimics the entactogenic effect of MDMA well [6], later with m-CPP (meta-chlorophenylpiperazine) (**16**), often combined with antiemetic substances like metoclopramide (**17**) and domperidone (**18**).

These adaptations clearly demonstrate, that the producers of such 'alternatives' are skilled and well educated and have detailed knowledge on pharmacology. Furthermore it can be seen in many forums that high level discussions on the creation of other designer drugs and their expected pharmacological effects take place.

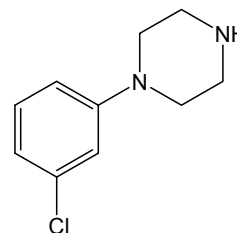
Although the piperazines found a stable place among the entactogenic designer drugs, a revival of MDMA is to be expected. Even though PMK as the preferred precursor is effectively banned in many countries, the precursor of PMK, PMK-glycidate (methyl 3-[3',4'-(methylenedioxy)phenyl]-2-methyl glycidate), a white solid is found more often in clandestine laboratories and is not yet banned by most of the current drug laws [7].



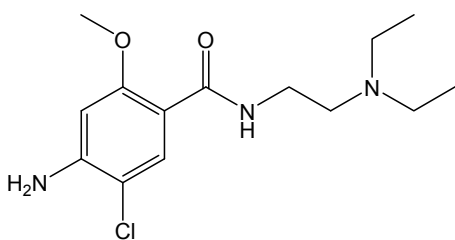
**(14)**  
BZP  
1-Benzylpiperazine



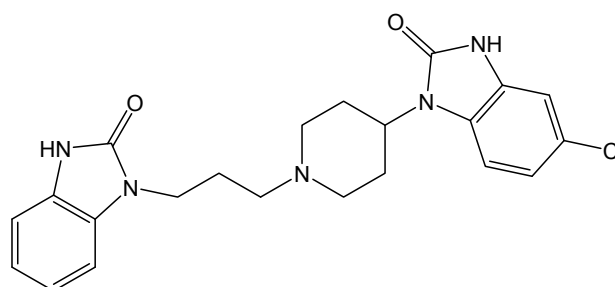
**(15)**  
TFMPP  
3-Trifluoromethyl-  
phenylpiperazine



**(16)**  
m-CPP  
meta-Chlorophenylpiperazine



**(17)**  
MCP  
Metoclopramide



**(18)**  
Domperidone

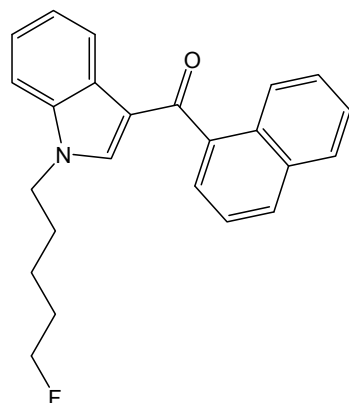
On the other hand there are seizures showing that also non-scientists with very little scientific or chemical background are involved in the 'business'. Demonstrated by an example of a seizure of 'XTC-tablets' containing Mecoprop as only active ingredient. Mecoprop is abbreviated as MCPP, but is a herbicide and has nothing to do with m-CPP, the **meta-chlorophenylpiperazine**.

### 3.5. Class of synthetic cannabinoids

With 'Spice' in early 2007 the first synthetic cannabinoids appeared in herbal mixtures in Switzerland. Figure 1 shows the variety of the synthetic cannabinoids with several subclasses. The 'JWH'-class alone consists of several hundred compounds as indicated by their number i.e. JWH-251.

Many of these synthetic cannabinoids are far more potent than THC itself. From HU-210 an around 600 fold stronger<sup>1</sup> CB-1 affinity is reported [8,9]. Since December 2010, only 4 JWH's (JWH-018, JWH-019, JWH-073, JWH-250) and 4 CP's (CP 47,497 and its C6-, C8- and C9-homologues) are regulated by the Swiss drug law [10]. However, alternatives are long since on the market.

The continuing development of new such substances can be demonstrated with recently encountered compounds of the 'JWH-next generation' e.g. 1-(5-fluoropentyl)-3-(1-naphthoyl) (AM-2201) (19). This is a fluoro derivative of JWH-018, which has not been published by John W. Huffman (Clemson University).



**(19)**  
AM-2201  
1-(5-fluoropentyl)-3-(1-naphthoyl)indole

### 3.6. Legal aspects

The current Swiss narcotics act and the corresponding regulations were hardly prepared for the appearance of the mentioned diversity of new designer drugs since 2007. As a matter of fact these designer drugs slip not only through the net of the narcotics act, also the medicines act, the food act and the chemicals act can only be applied in rare cases for the seizure of designer drugs. However, depending on the legislation, designer drugs can be considered as dangerous substances as a consequence of their uncontrolled production. They are considered a health risk for consumers and as a measure of protection the police can seize such substances to prevent an “immediate danger”.

<sup>1</sup> Other reports vary from 100 – 800 fold stronger effect

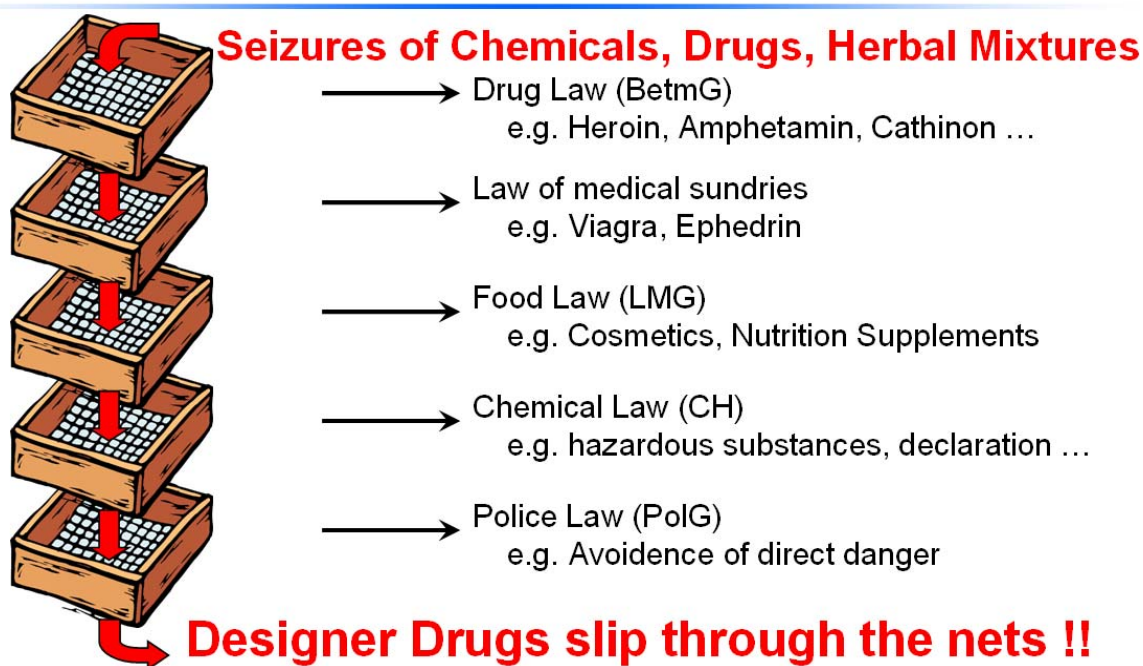


Fig. 2. Applicable laws for designer drugs.

In other words the legal situation remains unsatisfactory. With enacting the revised narcotics act and its regulations (presumably in July 2011) a new more effective tool will be created with an additional 'schedule e'. In this schedule, with an expected time delay of about 3 month, new appearing designer drugs can be listed. Further seizures of these compounds can then be treated under the narcotics act.

The revised narcotics act will permit the introduction of “generic clauses”, i.e. not only single substances but whole substance classes can be scheduled. Discussion about this issue are in progress and a first introduction of a generic clause is to be expected by the end of 2011.

### 3.7. Analytical data exchange

After a seizure of unknown material at the customs or the police, its immediate identification (including substitution pattern) by chemical analysis in the forensic laboratory is mandatory. Due to the lack or the poor availability of corresponding mass spectra or commercial reference materials, this task is very challenging. Therefore it should be one of the top priorities within the national and international drug working groups (“Gesellschaft für Toxikologie und Forensische Chemie” (GTFCh) “Arbeitskreis Suchtstoffe”, “European Network of Forensic Science Institutes” Drugs Working Group (ENFSI) Drugs Working Group, “European Monitoring Centre for Drugs and Drug Addiction” (EMCDDA), “Scientific Working Group Drugs” (SWGDRUG)) to cooperate and establish tools for a fast mass spectra exchange process.

Few but very valuable commercial and non commercial mass spectral databases already exist and are upgraded periodically [11-15]. However, the time delay of the distribution of a verified mass spectrum to the community is the critical factor and upgrades of commercial databases on an yearly bases are not sufficient.



#### 4. Conclusion

Designer drugs, research chemicals or so called “legal highs” are developing rapidly. The current narcotics act and corresponding regulations in Switzerland like in many other countries are not yet prepared to handle these substances and products on the illegal market adequately. An alignment of the legal situation is overdue and absolutely imperative. The only pragmatic way to achieve this goal is to include a generic clause of problematic substance classes in addition to the existing register of single substances. Should a single substance within such a class be used in a credible industrial process or as a medicament, this substance can be excluded or the producing company can be authorized to handle this substance. Any private and non credible use will then be considered as misuse of drug.

The forensic community is forced to rapidly coordinate and establish tools to identify new designer drugs and share its analytical data – especially mass spectra. The commercial producers of drug reference materials and mass spectral libraries are challenged to include new designer drugs in their product lists as soon as possible after the appearance on the illegal drug market.

#### 5. References

- [1] [http://www.drugs-forum.com/forum/showwiki.php?title=Category:Research\\_Chemicals](http://www.drugs-forum.com/forum/showwiki.php?title=Category:Research_Chemicals)
- [2] Several companies who produce designer drugs are known to the authors but are not cited here on purpose. For further details please contact the authors.
- [3] Nichols D, Brewster W, Johnson M, Oberlender R, Riggs R, Nonneurotoxic tetralin and indan analogues of 3,4-(methylenedioxy)amphetamine (MDA). *Journal of Medicinal Chemistry* 1990;33 (2): 703–10 and <http://en.wikipedia.org/wiki/MDAT>
- [4] <http://en.wikipedia.org/wiki/Methiopropamine>
- [5] <http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cathinones/de>
- [6] Baumann M, Clark R, Budzynski A, Partilla J, Blough B, Rothman R. N-substituted piperazines abused by humans mimic the molecular mechanism of 3,4-Methylenedioxy-methamphetamine (MDMA or ‘Ecstasy’). *Neuropsychopharmacology* 2005;30:550–60
- [7] Europol, Alert Report 2010-001, Releasable to Law Enforcement Only
- [8] <http://www.bluelight.ru/vb/showthread.php?t=279987>  
<http://www.drugs-forum.com/forum/showthread.php?t=117873>
- [9] ACMD report on the major cannabinoid agonists - [www.namsdl.org/documents/ACMDMajorCannabinoidReport.pdf](http://www.namsdl.org/documents/ACMDMajorCannabinoidReport.pdf)
- [10] <http://www.admin.ch/ch/d/sr/8/812.121.2.de.pdf>
- [11] Maurer H, Pflieger K, Weber A Mass Spectral and GC Data of Drugs, Poisons, Pesticides, Pollutants and Their Metabolites. *Mass Spectral and GC Data of Drugs, Poisons, Pesticides, Pollutants and Their Metabolites*. Wiley-VCH, Weinheim, ISBN: 978-3-527-32398-2
- [12] Rösner P, *Mass Spectra of Designer Drugs*, Wiley, ISBN: 3527328335
- [13] European Network of Forensic Science Institutes (ENFSI), Drugs Working Group is a closed user group for members <http://www.enfsi.eu/page.php?uid=56>
- [14] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), <https://ednd-cma.emcdda.europa.eu/>, closed user group
- [15] Scientific Working Group Drugs (SWGDRUG), Drugs Enforcement Agency United States, <http://www.swgdrug.org/tools.htm>