The Challenges of Analytical Method Validation of Designer Drugs in Non-Biological Samples by GC/MS

Fran Diamond    Technical Leader – Criminalistics Chemistry
May 15, 2012
Analysis of designer stimulants in the Forensic Analytical Laboratory
Hallucinogens have been used in some cultures for centuries. Amphetamines became popular initially in the 1930s and had a re-emergence in the 1960s. 1960s Mescaline and LSD have new popularity. MDMA emerged in the 1980s in a wave of new designer drugs that appeared. Most of them had been previously synthesized and studied.

- PIHKAL is an acronym that stands for “Phenethylamines I Have Known And Loved”.

New variations start showing up in Europe in 2007.
Initial wave hits United States in 2009.
Many states move to ban these substances.
As of Oct 21, 2011, MDPV, methylone and mephedrone have been temporarily controlled federally as schedule I controlled substances.
1980’s
α-methylnfentanyl, MPPP, MDMA,
1990’s, early 2000’s
PMA, rise of methamphetamine
1991 Publication of PiHKAL
1997 Publication of TiHKAL
“Combat Methamphetamine
Epidemic Act of 2005”
Growth of the Internet
Beginnings of the “Research
Chemicals” or “New Psychedelic”
Movement.
Designer Stimulants

- Not picked up in standard urine drug test. Compounds may be detected but not identified
- Legal Status
- Many outlets
  - Headshops
  - Mini-marts
  - internet
- Many distributors

“bath salts”
“Plant Food”
“Party Powders”
Designer stimulants— the new wave of synthetic drugs
Designer stimulants— the new wave of synthetic drugs
Designer stimulants– the new wave of synthetic drugs

- Marketed as:
  - Legal
  - Free over night shipping
  - Volume discounting
  - Buy four get fifth one free
  - Major credit cards accepted
  - Sold as “bath salts”, “Plant food”.
Designer Stimulants– the challenge

- Many drug-user websites are devoted to supporting the use of these substances.
  - Suggested dosages not accurate
  - Positive experiences reported
  - Enhances music, sex, Cinema, etc.
Designer Stimulants
Designer Drugs

2009-2011

Designer drugs - Structures

Cathinones  Examples

- Methylone
- Buphedrone
- Mephedrone

2-amino-1-phenyl-propan-1-one
Formula Weight: 149.190(7)
Exact Mass: 149.084063980(5)
Formula: C₅H₉NO
Composition: C 72.5% H 7.4% N 9.4% O 10.7%
Designer drugs - Structures

**Benzylpiperazines**

![Structure of 1-benzylpiperazine]

1-benzylpiperazine
Formula Weight: 176.258(9)
Exact Mass: 176.131348524(7)
Formula: C$_{11}$H$_{16}$N$_2$
Composition: C 75.0% H 9.1% N 15.9%

**Examples**

- Benzylpiperazine
- Trimethylfluoropiperazine
- oCCP
- mCCP
Designer drugs - Structures

Phenethylamines

2-phenylethylamine
Formula Weight: 121.180(6)
Exact Mass: 121.089149358(4)
Formula: C_8H_{11}N
Composition: C 79.3% H 9.1% N 11.6%

Examples

- Amphetamine
- Methamphetamine
- Phentermine
- 2C-E (2,5-dimethoxy-4-ethylphenethylamine)
- (DOB) 2,5-dimethoxy-4-bromoamphetamine
Designer drugs - Structures

Tryptamines

Examples

- Alpha-methyl tryptamine
- 5-Methoxy-Diallyltryptamine
- Psilocin
- Dimethyltryptamine
- 5-methoxy-N, N-diisopropyltryptamine

2-(1H-indol-3-yl)ethanamine
- Formula Weight: 160.216(8)
- Exact Mass: 160.100048396(5)
- Formula: C_{10}H_{12}N_{2}
- Composition: C 75.0%  H 7.5%  N 17.5%
Designer drugs - Structures

Pyrrolidinophenones

1-phenyl-2-pyrrolidin-1-yl-pentan-1-one

Examples

α-Pyrrolidinopentiophenone

α-Pyrrolidinopropiophenone

3',4'-Methylenedioxy-α-pyrrolidinobutiophenone

MDPV

Formula Weight : 231.33(1)
Exact Mass : 231.162314301(9)
Formula : C\textsubscript{15}H\textsubscript{21}NO
Composition : C 77.9%  H 9.1%  N 6.1%  O 6.9%
Lack of oversight
- “Not for human consumption” means no FDA intervention.

Lack of Quality Control
- This month’s “Ivory wave” may not be last month’s
- No accountability
- No guarantee of purity

Availability
- Large number of internet sites providing these products

Marketing
- Legal (you’ll pass your drug test)
- Safe
- Cheap
- Readily available
Designer Stimulants – the problem

- Health risks
  - rapid heart rate
  - high blood pressure
  - impaired perception
  - Sweating
  - reduced motor control
  - Disorientation
  - prolonged panic attacks
  - psychosis and violent episodes.
An Alarming New Stimulant, Legal in Many States

So-called bath salts are labeled “not for human consumption,” which helps them skirt a law that would make them illegal.

By ABBY GOODNOUGH and KATIE ZEZIMA
Published: July 16, 2011
Designer Stimulants— the problem escalates

U.S. Poison Centers Raise Alarm about Toxic Substance Marketed as Bath Salts; States Begin Taking Action

ALEXANDRIA, VA. – U.S. poison centers have taken 1,196 calls regarding toxic products marketed as “bath salts” so far this year, showing that public health threat presented by the products has yet to abate.

Poison centers took 298 calls in 2010 about the products, which doctors and clinicians at U.S. poison centers say cause increased blood pressure, increased heart rate, agitation, hallucinations, extreme paranoia and delusions. In 2011 alone, poison centers representing 45 states and the District of Columbia have received calls about these products.

On Thursday, Jan. 6, Louisiana Gov. Bobby Jindal announced he was classifying the substances as a Schedule 1 drug in Louisiana, meaning selling, buying, or possessing the substances would incur the same legal penalties as someone selling, buying or possessing heroin. Since then, the state of Florida has followed suit, issuing an emergency order criminalizing possession of the substances.

Mark Ryan, director of the Louisiana Poison Center, said the substances are the worst he has seen in 20 years at the poison center.
Designer Stimulants– the problem escalates

Designer Drugs Labeled as “Bath Salts”: Statistics on Abuse in New Jersey
Source: NJ Poison Information and Education System (NJPIES)

Reported Cases of Use by Month (as of April 20, 2011):

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<thead>
<tr>
<th>Month</th>
<th>Percent of Exposure Cases</th>
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<tbody>
<tr>
<td>January</td>
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<td>March</td>
<td>17.4%</td>
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<td>April*</td>
<td>52.2%</td>
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</table>
Designer Stimulants

The analytical challenge facing police labs

Detecting New Synthetic Drugs

Forensic labs in the United States should be better equipped to identify a new crop of recreational drug mimics.

By Cristina Luiggi | September 1, 2011

Underequipped and inadequately staffed forensic laboratories around the United States are likely to miss the new class of synthetic drugs that are cropping up, mostly in China, said chemists at the American Chemical Society meeting in Denver, Colorado. The drugs, which are synthesized to mimic existing illegal substances while evading detection, represent a growing problem worldwide. Detecting them requires laboratories to have a pure sample for comparison using analytical techniques such as gas-chromatography mass spectrometry.

"If you’re doing GCMS on a sample and it almost matches mephedrone, well maybe it’s butylone [a psychedelic drug used in research]," said Robert Lantz from the Rocky Mountain Instrumental Laboratories at the meeting. "A good analytical chemist would be able to say ‘yes, this is a slight variation’ as opposed to a button pusher who would simply say ‘it doesn’t match anything in my library’. (Hat tip to Nature News)"
Designer Stimulants

Published online 31 August 2011 | Nature | doi:10.1038/news.2011.513

Chemical shortage hampers 'legal high' work

Identification of suspect substances depends on reference materials that are in short supply.

Daniel Cressey

Attempts to understand and control new synthetic recreational drugs are being hindered by analysis laboratories' inability to obtain pure samples of the compounds, experts say.

The growing problem of synthetic drugs — which include mimics of cannabis and amphetamine — came to the fore in the United Kingdom last year as politicians rushed to ban mephedrone, which had been linked in the media to several deaths. Mephedrone and several related compounds, known collectively as cathinones, are now controlled substances in the United Kingdom and in many other countries. But new drugs are already appearing that circumvent these bans.

'Legal highs' such as mephedrone can be easily purchased over the Internet, but pure reference samples are hard to find.

Andy Rain/EPA/Corbis
**Designer Stimulants—numerous possibilities**

<table>
<thead>
<tr>
<th>Designer Stimulants</th>
<th>Piperazines</th>
</tr>
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<tbody>
<tr>
<td>Cathinones</td>
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<tr>
<td>4-MMC</td>
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<tr>
<td>Methcathinone</td>
<td>TFMPP</td>
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<tr>
<td>MDVP</td>
<td>pCPP</td>
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<tr>
<td>Methylenedioxymethcathinone</td>
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<td>alpha-PVP</td>
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<td>4-HO-MPT</td>
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**Designer Stimulants**

- Cathinones: 4-methylmethcathinone, 2-(methylamino)-propiophenone, 3,4-methylenedioxymethcathinone, N-methylcathinone, 3,4-methylenedioxy-N-ethylcathinone
- Piperazines: BZP, TFMPP, pCPP, oCPP, mCPP, N-methylcathinone, N-ethylcathinone, 4-Chlorophenylpiperazine, 2-Chlorophenylpiperazine, 3-Chlorophenylpiperazine

**Phenethylamines**

- Cathine, β-hydroxy-amphetamine
- Cathinone, β-keto-amphetamine
- Methcathinone, N-methylcathinone
- Mephedrone, 4-methylmethcathinone
- Ethcathinone, N-ethylcathinone
- Amphetamine, o-methylphenylethylamine
- Methamphetamine, N-methylamphetamine

**Tryptamines**

- Bufotenin, 5-hydroxy-N,N-dimethyltryptamine
- DMT, N,N-dimethyltryptamine
- 5-MeO-DMT, 5-methoxy-N,N-dimethyltryptamine
- NMT, N-methyltryptamine
- Psilocin, 4-hydroxy-N,N-dimethyltryptamine
- AET, α-ethyltryptamine
- AMT, α-methyltryptamine
- DALT, N,N-diallyltryptamine
- DET, N,N-diethyltryptamine
- DiPT, N,N-diisopropyltryptamine
- DPT, N,N-dipropyltryptamine
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- 4-HO-DiPT, 4-hydroxy-N,N-diisopropyltryptamine
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- 5-MeO-DiPT, 5-methoxy-N,N-diisopropyltryptamine
- 4-HO-MPT, 4-hydroxy-N-isopropyl-N-methyltryptamine
NMS labs Forensic Services

We work hard to develop advanced tests to meet emerging needs of:

- Medical Examiners
- Coroners
- Crime Labs
- Law Enforcement
- Attorneys
- Government Agencies
- Private Corporations

With NMS Labs as your partner, you can confidently receive timely and authoritative results that withstand the most challenging judicial and scientific review.
NMS Labs Overview

- **Invested in Quality**
  - LEAN increases capacity and service levels
  - CQI—Continuous Quality Improvement

- **Quality of Testing Confirmed by Licenses & Accreditations**
  - NMS Labs holds nearly 20 licenses & accreditations obtained via federal and state agencies and quality organizations
  - OSHA, CLIA, CAP, ABFT, ASCLD/LAB-International

- **Demonstrated Commitment to R&D**
  - Growing high-caliber scientific staff with highly recognized credentials
  - Newest technologies [molecular diagnostics, LC-MS/MS]
  - New tests, customized panels [new drugs, endocrinology]
Designer Stimulants– initial validation

- Interest from the South and Midwest where the problem first hit the U.S.
- Samples start to come in-house.
- Analyze by GC/MS. Search multiple databases.
- Samples contain unidentified spectra.
- Examine fragmentation
  - Base peak
  - Molecular ion
- Analyze by TOF for molecular formula information.
- Research items and obtain any available materials from various sources.
Designer Stimulants– unknown spectrum
Designer Stimulants – identification

3,4-Dimethymethcathinone

Formula Weight: 191.27(1)
Exact Mass: 191.131014173(7)
Formula: C₁₂H₁₇NO
Composition: C 75.4% H 9.0% N 7.3% O 8.4%
Designer Stimulants– initial validation

- Obtain designer drug mass spectral database.
  - Wiley Mass Spectra of Designer Drugs 2011
- Obtain reference material (when possible)
- Custom synthesis of some materials
- Build a database of emerging substances
- Continuous research (i.e. internet browsing) for the next wave of drugs.
- Observe additional unknown peaks.
Partner with custom synthesis companies. A costly venture.

They provide Certificate of analysis which includes NMR, purity (HPLC), mass spectrum, appearance, water wt., etc.

Standard material is characterized in-house by GC/MS, TLC, LC/MS TOF (for exact mass).

Spectra are searched via commercially available databases.

Consultation with experts in the field. Many of them from Europe where the problem initiated.

Build a database with retention time data.
Designer Stimulants—reference material sources

- Cerilliant corporation
  - [http://www.cerilliant.com/](http://www.cerilliant.com/)
- Cayman Chemical
- LGC standard
  - [http://www.lgcstandards.com/epages/LGC.sf](http://www.lgcstandards.com/epages/LGC.sf)
- Lipomed
- Toronto Research chemical
- Sigma Aldrich
### Results Of Analysis Tests

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<tr>
<th>Tests</th>
<th>Analysis Standard</th>
<th>Results</th>
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<tr>
<td>Description</td>
<td>A white powder</td>
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<tr>
<td>Loss On Drying</td>
<td>NMT 1.2%</td>
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<td>Assay</td>
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<tr>
<td>AKA.</td>
<td>Geranamine(DMAA)</td>
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</tr>
</tbody>
</table>

**Conclusion:** This batch meets all export standards.

**Q.C.Dept. Director:** Tom  
**Checker:** Linda  
**Identifier:** Tiffany
Designer Stimulants—reference databases

- NIST11
- Wiley Designer drug
- Cayman Chemical Company
- AAFS
- SWGDRUG
- Pfleger
- Your in-house database
- Dr. Peter Rösner (Designer Drugs Online)
- RTI (Research Triangle Institute) drug database
- Southern Association of Forensic Scientists.
Temporary Scheduling
3/1/2011 – Synthetic Cannabinoids

- JWH-018
- JWH-073
- JWH-200
- CP47,497 (C7)
- CP47,497 (C8)

10/21/2011 “Bath Salts”

- MDPV
- Mephedrone
- Methylone
Designer Stimulants– legal status

- Current status:
  - Controlled by the DEA as of Oct 2011
    - Mephedrone
    - MDPV (3,4 methylenedioxypyrovalerone)
    - Methylone
  - Many states and local municipalities have broader bans in effect. States tend to list the specific additional substances in their ban.
  - At the federal level, the Controlled substances act serves to render many additional compounds as banned substances.
Designer Stimulants– what’s legal-what isn’t?

Methylone-illegal

Ethylone-legal
Designer stimulants - Legal Status

The Federal Analogue Act defines an analog as a substance which is 'substantially similar' to a scheduled substance and has either an effect 'similar to or greater than' a controlled substance or is thought to have such an effect.

21 U.S.C. § 813
Designer Stimulants—similar mass spectra

Methylenedioxymethamphetamine (MDMA)

3,4-dimethylmethcathinone

#10: Methylenedioxymethamphetamine (MDMA)

#8: 3,4-Dimethylmethcathinone
Designer Stimulants— similar mass spectra

**Butylone**

**Ethylone**
Designer Stimulants– development

- Data analysis
  - Customized database for native compounds
  - Commercial database for unknowns
  - Isomeric pairs
  - Simple spectra with few unique fragments
  - Many compounds
  - Samples are mixtures with many different drugs
  - Precursor molecules present
Designer Stimulants—development

- Items for development
  - Sample preparation/extraction
  - Acquisition
  - Data analysis
    - Largest Challenge
      - Isomeric pairs
      - Co-eluting molecules
      - Simple Mass Spectra
      - Common base peaks (m/z 58, 72, 44, etc.)
Designer Stimulants—development

- **Sample extraction**
  - These are simple organic molecules. Mostly amino-compounds that will extract under alkaline conditions.
  - Acid/base extraction
  - Sample preparation generally not problematic
  - Derivatization may be necessary at trace concentration
Designer Stimulants– development

- **Acquisition**
  - Agilent 5973N-turbo mass spectrometer
  - Gas Chromatograph: 6890, autoinjector and tray
  - DB-1 column (pt# 128-1012)
    - 12 meter
    - 0.2 mm i.d.
    - 0.33 um film thickness
  - Helium Flow: 2.6 mL/min.
  - Constant pressure
  - Ramp: 50 - 340°C. @ 30°/min.
  - Scan range: 40 – 550 amu
GC/MS - combined total ion chromatograms
LC-TOF in the testing laboratory
LC-TOF – designer drugs
<table>
<thead>
<tr>
<th></th>
<th>compound</th>
<th>RRT</th>
<th>RRT-2</th>
<th>Ions</th>
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<th>compound</th>
<th>RRT</th>
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<td>45</td>
<td>42</td>
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</table>
Deconvolution with retention time matching

Ions with the same abundance vs time profile are grouped together to create spectra “cleaned” of interferences from overlapped peaks.

Three Overlapped Chromatographic Peaks

Deconvolution

Interference 1

Interference 2

Target
Designer Stimulants—Validation work

- More prevalent findings
  - Methylone
  - MDPV
  - Ethylone
  - Naphyrone
  - 3,4-Dimethylmethcathinone
  - MDMA
  - Benzylpiperazine
  - TFMPP

- Butylone
- Pyrovalerone
- 4-Methylethcathinone
- 2C-E
- 2C-I
- Mephedrone
- 5-MeO-DALT

- Plus many more unidentified spectra
Designer Stimulants—summary

- Summary of challenges
  - Multiple analytes
    - Requires database of retention time and searchable spectra. This is an ever changing pool of drugs. Must be able to maintain and expand a dynamic database.
  - Similar analytes
    - Numerous isomeric and/or analogous compounds that require ability to measure slight differences in retention time and slight differences in mass spectra.
Designer Stimulants—summary

- **Items for validation**
  - Certified reference material
    - Reputable vendors
    - Custom synthesis with proper material characterization.
  - Quality database
    - Commercial peer-reviewed data
    - In-house with retention time data
    - Correct nomenclature
  - Acquisition method capable of performing the separation of closely related compounds.
  - Skilled chemists who know the science and the market.
Contact information

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