

Protected B

Record of Discussion (ROD)

Controlled Substances Scheduling (CSS) Working Group Meeting

Wednesday February 19th, 2011, 10:00-11:30am

123 Slater Street, Rm 505A

Present:	Regrets:
<ul style="list-style-type: none">• Suzanne Desjardins, Office of Research and Surveillance ,(ORS), Controlled Substances and Tobacco Directorate (CSTD), Healthy Environments Consumer Safety Branch (HECSB) (Chair)• Tiana Branch, OCS, CSTD, HECSB• Robin Marles, Bureau of Clinical Trials and Health Sciences, Natural Health Products Directorate (NHPD), HPFB• Courtney Smith, Border Integrity Unit, Health Products and Food Branch• Tiffany Thornton (Secretariat) ORS, CSTD, HECSB• Tanja Kalajdzic, Marketed Pharmaceuticals & Medical Devices Division, Health Products and Food Branch (HPFB) via phone• Bruna Brands, ORS, CSTD, HECSB, via phone• Patricia Rapold, OCS, CSTD, HECSB	<ul style="list-style-type: none">• Hanan Abramovici, ORS, CSTD, HECSB• Denis Arsenault, OCS, CSTD, HECSB• Colette Strnad, Office of Science, Therapeutic Products Directorate (TPD)• Evelyn Soo, ORS, CSTD, HECSB

1. Welcome & Introductions

Suzanne welcomed the working group members.

2. Approval of Agenda Items

Agenda approved.

3. Approval of ROD from January 19th, 2011

The ROD for Tuesday, January 19th, 2011 was approved.

4. Discussion and Review of Inclusion and Exclusion Criteria of EAC Involvement in the Scheduling Process

CSS-WG members decided that the following changes would be made to the CDSA scheduling process map:

- An additional decision diamond would be added before the Public/Stakeholder Consultation box, in order to reflect the decision on whether the criteria for public/stakeholder consultation have been met.
- The second decision diamond related to EAC criteria would be reworked in order to more clearly reflect that if the criteria are not met, the EAC would be consulted.
- The process map should focus solely on the CDSA scheduling process. Therefore, Step 7B (and its associated boxes related to the FDR process) would be removed. Instead, the process map should include an additional decision diamond indicating that if the decision is made to schedule a substance contained in a pharmaceutical/therapeutic product under the CDSA, the CSS-WG will advise the HPFB Drug Scheduling Status Committee.

Once the process map is revised it was agreed that it would be helpful to use a substance that was controlled for public safety or other scheduling criteria to test as an example through the process map.

5. Update on Other Items relevant to the CSS-WG

- It's Your Health on *Salvia divinorum* is scheduled for release on Health Canada's website (<http://hc-sc.gc.ca/hl-vs/iyh-vsv/life-vie/salvia-eng.php>). This will coincide with the NOI and Health Canada's intention to make it illegal to produce, traffic, possess, import or export *Salvia divinorum* and its active ingredient salvinorin A.
- Robin followed up on his inquiry made at the meeting in February about the status of the legal inquiry previously made by OCS regarding hemp oil. Tiana indicated that she would speak with Denis about the outstanding legal opinion on this issue.

Actions:

- Denis to follow-up with the Department's legal services in order to obtain a response.

- Suzanne indicated that she has been invited to present at the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) First International Forum on New Drugs in May 2011. While the exact details of the presentation have not been confirmed, Suzanne indicated that it this may be an opportunity to highlight our scheduling process.

Actions:

- Suzanne will keep the CSS-WG informed regarding the development of the presentation
- Suzanne indicated that there has been some attention lately regarding both mephedrone and methylenedioxypropylamphetamine (MDPV) being sold as “bath salts” and “plant food” which some people are using because of their stimulant properties. At the present time, mephedrone is controlled in Canada and also in the UK, however only in some states in the US. MDPV is not controlled in Canada. Health Canada has prepared media lines regarding Mephedrone.
- Robin indicated that HPFB’s Health Risk Assessment was finalized at the Branch Executive Committee meeting in October of 2010. Upcoming training sessions will be held by HPFB and it might be helpful for a member of the CSS-WG to attend. Suzanne suggested that Hanan could attend depending on his availability.

Actions:

- Robin to send the training session information to Tiffany to forward to Hanan.

5. Next Steps:

Tiffany to circulate the invitation, agenda and ROD for the next meeting on Wednesday March 16th, 2011

s.21(1)(b)



Fw: Revised Agenda: CSS-WG Meeting March 14th

Andre Fouquet, Ann Kourtesis, Bruna

Tiffany Thornton to: Brands, Claudia Campos, Colette Strnad,
Denis Arsenault, Hanan Abramovici, Helmi

2012-03-13 01:22 PM

Cc: Laura Cooney, Erin Rutherford

Please note the revised agenda - additional item added(item #6 with background info attached below).

See you tomorrow,
Tiffany

Draft Agenda:

- 1- Members' introduction
- 2- Approval of agenda
- 3 - Approval of ROD from October 2011 (attached)
- 4 - Update on [REDACTED] Tanja & OCS)
- 5 - Update on MDPV (Evelyn)
- 6- Update on the WHO 35th Expert Committee on Drug Dependence - see agenda for the meeting attached (Bruna)
- 7 - Update/s on any issues relevant to the WG's activities
 - membership (new members)
 - monthly meetings (every 3rd Wed)
 - other?

----- Forwarded by Tiffany Thornton/HC-SC/GC/CA on 2012-03-13 01:16 PM -----



**World Health
Organization**

**35th Expert Committee on Drug Dependence (ECDD)
4-8 June 2012, Hammamet, Tunisia**

Provisional Agenda

1. OPENING OF MEETING
2. PROCEDURAL MATTERS
 - 2.1 Election of chairperson, vice-chairperson and rapporteur
 - 2.2 Adoption of agenda
3. FOR INFORMATION OF THE COMMITTEE
 - 3.1 Revision of Guidelines
 - 3.2 Work of international bodies concerned with controlled substances
4. CRITICAL REVIEW OF PSYCHOACTIVE SUBSTANCES

000004

4.1 GHB¹

4.2 Ketamine INN²

5. PRE-REVIEW

5.1 Dextromethorphan pINN³

5.2 Tapentadol⁴

5.3 Piperazines⁴

N-benzylpiperazine (BZP),
1-(3-trifluoromethyl-phenyl)piperazine (TFMPP),
1-(3-chlorophenyl)piperazine (mCPP),
1-(4-methoxyphenyl)piperazine (MeOPP) and
1-(3,4-methylenedioxybenzyl)piperazine (MDBP)

5.3 Gamma-butyrolactone¹

5.4 1,4-Butanediol¹

6. OTHER ISSUES

6.1 Use of terms⁴

6.2 Use of pharmacovigilance data for the assessment of dependence and abuse potential
(procedures and methodology)¹

6.3 Balancing medical availability and prevention of misuse of medicines manufactured
from controlled substances¹

6.4 Improving the evidence base of substance evaluation⁴

7. ADOPTION OF REPORT

8. CLOSURE OF MEETING

¹ decided by 34th ECDD

² pending from 34th ECDD

³ proposed by an expert

⁴ proposed by the Secretariat

Tiffany Thornton

Hi, Please find the revised agenda with the addit...

2012-03-13 08:22:38 AM

From: Tiffany Thornton/HC-SC/GC/CA
To: Evelyn Soo/HC-SC/GC/CA@HWC
Cc: Andre Fouquet/HC-SC/GC/CA@HWC, Ann Kourtesis/HC-SC/GC/CA@HWC, Bruna
Brands/HC-SC/GC/CA@HWC, Claudia Campos/HC-SC/GC/CA@HWC, Colette
Strnad/HC-SC/GC/CA@HWC, Denis Arsenault/HC-SC/GC/CA@HWC, Hanan
Abramovici/HC-SC/GC/CA@HWC, Helmi Hussien/HC-SC/GC/CA@HWC, Jocelyn
Kula/HC-SC/GC/CA@HWC, Richard Laing/HC-SC/GC/CA@HWC, Robin
Marles/HC-SC/GC/CA@HWC, Stephanie Chandler/HC-SC/GC/CA@HWC, Suzanne
Desjardins/HC-SC/GC/CA@HWC, Tanja Kalajdzic/HC-SC/GC/CA@HWC
Date: 2012-03-13 08:22 AM
Subject: Re: Agenda: CSS-WG Meeting March 14th

Hi,
Please find the revised agenda with the additional items added.

Thanks,
Tiffany

Draft Agenda:

- 1- Members' introduction
- 2- Approval of agenda
- 3 - Approval of ROD from October 2011 (attached)
- 4 - Update on ██████████ (Tanja & OCS)
- 5 - Update on MDPV (Evelyn)
- 6 - Update/s on any issues relevant to the WG's activities
 - membership (new members)
 - monthly meetings (every 3rd Wed)
 - other?

Evelyn Soo Hi Tiffany I would also like to add MDPV to the a... 2012-03-12 04:53:35 PM

From: Evelyn Soo/HC-SC/GC/CA
 To: Tiffany Thornton/HC-SC/GC/CA@HWC
 Cc: Andre Fouquet/HC-SC/GC/CA@HWC, Ann Kourtesis/HC-SC/GC/CA@HWC, Bruna Brands/HC-SC/GC/CA@HWC, Claudia Campos/HC-SC/GC/CA@HWC, Colette Strnad/HC-SC/GC/CA@HWC, Denis Arsenault/HC-SC/GC/CA@HWC, Hanan Abramovici/HC-SC/GC/CA@HWC, Helmi Hussien/HC-SC/GC/CA@HWC, Jocelyn Kula/HC-SC/GC/CA@HWC, Richard Laing/HC-SC/GC/CA@HWC, Robin Marles/HC-SC/GC/CA@HWC, Stephanie Chandler/HC-SC/GC/CA@HWC, Suzanne Desjardins/HC-SC/GC/CA@HWC, Tanja Kalajdzic/HC-SC/GC/CA@HWC
 Date: 2012-03-12 04:53 PM
 Subject: Re: Agenda: CSS-WG Meeting March 14th

Hi Tiffany

I would also like to add MDPV to the agenda if possible.

Thanks
Evelyn

Evelyn C Soo, PhD
 A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
 Office of Research and Surveillance | Bureau de la recherche et de la surveillance
 Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
 environnementale et de la sécurité des consommateurs (DGSESC)
 Health Canada | Santé Canada
 123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
 evelyn.soo@hc-sc.gc.ca
 Telephone | Téléphone 613-954-1758
 Government of Canada | Gouvernement du Canada

Tiffany Thornton Hi everyone, In preparation for Wednesday's me... 2012-03-12 03:20:36 PM

From: Tiffany Thornton/HC-SC/GC/CA

s.21(1)(b)

To: Andre Fouquet/HC-SC/GC/CA@HWC, Bruna Brands/HC-SC/GC/CA@HWC, Colette Strnad/HC-SC/GC/CA@HWC, Denis Arsenault/HC-SC/GC/CA@HWC, Evelyn Soo/HC-SC/GC/CA@HWC, Hanan Abramovici/HC-SC/GC/CA@HWC, Jocelyn Kula/HC-SC/GC/CA@HWC, Richard Laing/HC-SC/GC/CA@HWC, Robin Marles/HC-SC/GC/CA@HWC, Stephanie Chandler/HC-SC/GC/CA@HWC, Tanja Kalajdzic/HC-SC/GC/CA@HWC, Ann Kourtesis/HC-SC/GC/CA@HWC, Claudia Campos/HC-SC/GC/CA@HWC, Helmi Hussien/HC-SC/GC/CA@HWC
Cc: Suzanne Desjardins/HC-SC/GC/CA@HWC
Date: 2012-03-12 03:20 PM
Subject: Agenda: CSS-WG Meeting March 14th

Hi everyone,

In preparation for Wednesday's meeting (March 14th) here is the draft agenda for the CSS-WG meeting. Please let me know if you have any further items to add. Should you wish to participate via teleconference please dial: 1-877-413-4792 conference code: 2134819.

Draft Agenda:

- 1- Members' introduction
- 2- Approval of agenda
- 3 - Approval of ROD from October 2011 (attached)
- 4 - Update on [REDACTED] (Tanja)
- 5 - Update/s on any issues relevant to the WG's activities
 - membership (new members)
 - monthly meetings (every 3rd Wed)

[attachment "Oct 19 - ROD draft doc.doc" deleted by Evelyn Soo/HC-SC/GC/CA]

Thanks,
Tiffany

----- Forwarded by Tiffany Thornton/HC-SC/GC/CA on 2012-03-12 03:12 PM -----

CSS-WG Meeting



2012-03-14 Wed 10:00 AM - 11:30 AM

Location: 123 Slater Street, 305A

Required:

Andre Fouquet/HC-SC/GC/CA@HWC, Bruna Brands/HC-SC/GC/CA@HWC, Colette Strnad/HC-SC/GC/CA@HWC, Denis Arsenault/HC-SC/GC/CA@HWC, Evelyn Soo/HC-SC/GC/CA@HWC, Hanan Abramovici/HC-SC/GC/CA@HWC, Jocelyn Kula/HC-SC/GC/CA@HWC, Richard Laing/HC-SC/GC/CA@HWC, Robin Marles/HC-SC/GC/CA@HWC, Stephanie Chandler/HC-SC/GC/CA@HWC, Suzanne Desjardins/HC-SC/GC/CA@HWC, Tanja Kalajdzic/HC-SC/GC/CA@HWC, Veronique Lalonde/HC-SC/GC/CA@HWC

Description

Please forward agenda items prior to the meeting. If you wish to participate via teleconference please let me know.

Thank you,
Tiffany Thornton
946-3590

Protected B Draft

Record of Discussion (ROD)
Controlled Substances Scheduling (CSS) Working Group Meeting
Wednesday, March 14 2012, 10:00-11:30am
123 Slater Street, Rm 305A

<p>Present:</p> <ul style="list-style-type: none">• Suzanne Desjardins, Office of Research and Surveillance (ORS), Controlled Substances and Tobacco Directorate (CSTD), (HECSB) (Chair)• Denis Arseneault, Office of Controlled Substances (OCS), CSTD, HECSB• Claudia Campos, Border Integrity Unit, HPFB via phone• Ann Kourtesis, Border Integrity Unit, HPFB via phone• Hanan Abramovici, ORS, CSTD, HECSB• Bruna Brands, ORS, CSTD, HECSB via phone• Colette Strand, Office of Science, Therapeutic Products Directorate, (TPD) via phone• Jocelyn Kula, OCS, CSTD, HECSB• Helmi Hussien for Robin Marles, Bureau of Clinical Trials and Health Sciences, NHPD, HPFB via phone• Tanja Kalajdzic, Marketed Pharmaceuticals & Medical Devices Division, (HPFB)• Evelyn Soo, ORS, CSTD, HECSB• David Duguay, Marketed Pharmaceuticals & Medical Devices Division, (HPFB)	<p>Regrets:</p> <ul style="list-style-type: none">• André Fouquet, Drug Analysis Service—Quebec Region, Regions and Programs Branch (RAPB)• Stephanie Chandler, OCS, CSTD, HECSB <p>Secretariat:</p> <ul style="list-style-type: none">• Tiffany Thornton (Secretariat) ORS, CSTD, HECSB
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1. Welcome & Introductions

Suzanne welcomed the working group members.

2. Approval of Agenda Items

Agenda items were approved.

s.20(1)(b)

3. Approval of ROD October 19th, 2011

ROD approved.

4. Update on [REDACTED]:

Tanja indicated that MHPD has been monitoring and evaluating adverse reaction data post market for [REDACTED]. Findings show:

- there has been a factor 9 increase in overdose between 2008-09 and 2010-11
- there has been a factor 7 increase in drug abuse between 2009-10 and 2010-11
- there has been a factor 6.8 in suicide between 2009-10 and 2010-2011

There has been a 13% decrease in exposure to [REDACTED] over the last year (2010-2011 vs 2009-2010), suggesting a reduction in the number of patients taking this medication and/or in the duration of the treatment.

Tanja inquired whether OCS plans to proceed with the process for scheduling on the CDSA. Jocelyn noted that despite this new evidence OCS has no current plans to proceed at this time, given other priorities.

Suzanne indicated that the drug is not scheduled on the CDSA nor the FDA. This is problematic as there seems to be no grounds to stop shipments at the border as personal importation is legal. For example, in December ORS was made aware that a large shipment of [REDACTED] came through the border however there were not any substantive grounds to withhold it. The Inspectorate will clarify the process in such circumstances. Claudia noted that usually when a large shipment of a non scheduled substance is released it is forwarded to domestic compliance for verification. She was not aware of the details of this specific case but would follow-up.

It was agreed by CSS WG members that MHPD should conduct further evaluation on spontaneous cases of [REDACTED] over the next 6-8 months to develop the evidence base.

Actions:

- Tanja will inform MHPD management about the CSS-WG recommendation to conduct further evaluations
- Claudia to follow up on the specific case in December and to clarify what criteria is used to hold non scheduled or regulated substance at the border
- Bruna will look into any international reports on [REDACTED] and provide an update

5. Update/s on MDPV

Evelyn indicated that MDPV (bath salts) is an ongoing issue of interest in the media and various stakeholder groups including the police in Atlantic Canada who inquired whether Health Canada plans to schedule MDPV on the CDSA.

Jocelyn noted that senior management has advised OCS to develop a work plan and proceed with a regulatory proposal. The sources of information/data to be drawn upon for the proposal could include: drug seizures, pharmacology, Inspectorate, controls used in other countries (US, Denmark, Sweden).

Actions:

- Bruna indicated that MDPV would be one of the agenda items discussed at the ECCD meeting in June and will follow up with WG upon her return
- OCS will draft a work plan and consult with ORS for support.

6. Update on the WHO 35th ECDD

Bruna shared the proposed agenda for the 35th ECDD on June 4-8th in Tunisia. dextromethorplan (an active ingredient in cough syrup) is included on the agenda. Bruna indicated that recent evidence suggests that this substance is a problem among young people who are using/abusing it as a hallucinogen. She is interested in how the decision was made to specifically exclude it from the CDSA.

Jocelyn stated that detromethorplan has been on the market since the 1960s and likely not included on the CDSA because there was limited knowledge on how it could be abused for psychotropic effects. Tanja asked Bruna send any scientific reviews on dextromethorplan that she may have for reference.

h

Actions:

- Bruna to send review articles discussing the abuse of Dextromethorplan to Tanja
- CSS-WG to provide any available information on dextromethorplan to Bruna before the ECCD meeting in June

7. Update/s on emerging issues

- CSS-WG agreed that effective April 2012 monthly meetings would take place every 3rd Wednesday from 1:30-3pm
- Suzanne to circulate a note confirming the representatives for the CSS-WG for each organization

8. Next Steps

- Tiffany to circulate the agenda and ROD from prior to the next meeting on April 18, 2012.

Re: question re MDPV 

Jocelyn Kula to: Suzanne Desjardins
Cc: Erin Rutherford

2012-03-20 09:25 AM

OK but I have to have a workplan to Johanne for Thurs noon Wed latest.

JK

Sent by blackberry

Suzanne Desjardins thanks for the clarification. I'll get back to yo... 2012-03-20 09:02 AM EDT

From: Suzanne Desjardins
To: Jocelyn Kula
Cc: Erin Rutherford
Date: 2012-03-20 09:02 AM EDT
Subject: Re: question re MDPV

thanks for the clarification. I'll get back to you this week with a firmer timeframe for our input.
Suzanne

Jocelyn Kula The Minister's Office wants it scheduled as soon... 2012-03-20 08:58:32 AM

From: Jocelyn Kula/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC
Cc: Erin Rutherford/HC-SC/GC/CA@HWC
Date: 2012-03-20 08:58 AM
Subject: Re: question re MDPV

The Minister's Office wants it scheduled as soon as possible and we are definitely going to be making a case for skipping CG I, and so would be looking to get something to TB for the beginning of the new parliamentary session in late September. At the latest. Of course, the Minister's Office could turn around and say not fast enough, late June is when it needs to be done but I am hoping that will not be the case....

I think the answer to your question re when we need ORS input is really dependent on what the shortest turnaround time for your part of the analysis is. From the quick review we have done, I would not say there are hundreds of papers to review....

Hope this helps.

JK

Sent by blackberry

Suzanne Desjardins Hi Jocelyn, Can you clarify what "expedited t... 2012-03-20 08:36 AM EDT

From: Suzanne Desjardins
To: Jocelyn Kula
Cc: Erin Rutherford
Date: 2012-03-20 08:36 AM EDT
Subject: Re: question re MDPV

Hi Jocelyn,

Can you clarify what "expedited timeline" means and when do you expect our input?

Thanks

Suzanne

Jocelyn Kula Great thanks. And the idea is to have ORS invol... 2012-03-19 09:56:25 PM

From: Jocelyn Kula/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC
Date: 2012-03-19 09:56 PM
Subject: Re: question re MDPV

Great thanks. And the idea is to have ORS involved right from the beginning.....this one just sprung up on us!

I'll wait to hear from you.

Jocelyn

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire

Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada/ Santé Canada

Tel: (613) 946-0125 Fax: (613) 946-4224

Suzanne Desjardins Hi Jocelyn, Ideally, we should be "more intima... 2012-03-19 04:25:18 PM

From: Suzanne Desjardins/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-03-19 04:25 PM
Subject: Re: question re MDPV

Hi Jocelyn,

Ideally, we should be "more intimately" involved from the beginning. it is often easier and faster to do it than review someone else's.

We could do " the review of pharmacology and abuse potential/addiction potential information" as well as contribute to the extent of actual use.

I'll get back to you tomorrow morning on our approach.

Thanks
Suzanne

Jocelyn Kula Hi there, I just saw you and forgot I had a questi... 2012-03-19 02:49:16 PM

From: Jocelyn Kula/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC
Date: 2012-03-19 02:49 PM
Subject: question re MDPV

Hi there,

I just saw you and forgot I had a question of my own for you! Wondering if you can advise what if any role ORS should play in the scheduling assessment of MDPV, and in particular, the review of pharmacology and abuse potential/addiction potential information. As I indicated at the CSS WG meeting last week, we are under extreme pressure from senior management to move on this scheduling assessment and get a

regulatory proposal together in an expedited timeline, and so I am wondering if you have someone that is currently free that could be assigned to this work or whether you would be looking at contracting it out, and if so, whether the additional value added of external review is worth the additional time to get that process in motion.

Presuming that we can get our hands on the assessments done by the US and the UK (I am more confident in terms of the US but we will certainly approach the UK), do you think OCS could do a first review and then ORS could provide its input at the time of the CSS WG review, or would you prefer to be more intimately involved?

I am to have a workplan to Johanne for first thing tomorrow, and so would appreciate your views as soon as possible.

Merci en avance
Jocelyn

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224



Re: availability for a short contract with Health Canada

Vlad Kushnir

to:

Erin Rutherford

2012-03-28 05:34 PM

Please respond to Vlad Kushnir

Show Details

2 Attachments



graycol.gif



MDPV Assessment Proposal - signed March 28, 2012.pdf

Hi Erin,

Please accept the signed proposal; I look forward to receiving a formal contract within the next little while.

I have recently attended a talk where MDPV intoxication was discussed as a new phenomenon presenting in hospital emergency rooms. I am therefore quite excited to be working on this project and guiding policy making in this capacity.

Best regards,

Vlad

From: Erin Rutherford <erin.rutherford@hc-sc.gc.ca>

To: Vlad Kushnir [REDACTED]

s.19(1)

Cc: Hanan Abramovici <hanan.abramovici@hc-sc.gc.ca>

Sent: Wednesday, March 28, 2012 11:37:58 AM

Subject: Re: availability for a short contract with Health Canada

Vlad,

Thanks very much - have confirmed that the revised timelines will be fine.

We will initiate the contracting process upon receipt of the signed proposal.

Thanks

Erin Rutherford

Manager/Gestionnaire
Drugs and Alcohol Research/Recherche, drogues et alcool
Office of Research and Surveillance / Bureau de la recherche et de la surveillance
Controlled Substances and Tobacco Directorate / Direction des substances
contrôlées et de la lutte au tabagisme
Healthy Environments and Consumer Safety Branch / Direction générale de la
santé environnementale et de la sécurité des consommateurs
Health Canada / Santé Canada

123 Slater, MacDonald Building
Room A616 Address Locator: AL 3506 D
Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210
Fax: (613) 952-5188
E-mail: erin.rutherford@hc-sc.gc.ca

Vlad Kushnir ---2012-03-26 03:00:46 PM---Good Afternoon Erin,

From: Vlad Kushnir [REDACTED]
To: Erin Rutherford <erin.rutherford@hc-sc.gc.ca>
Cc: Hanan Abramovici <hanan.abramovici@hc-sc.gc.ca>
Date: 2012-03-26 03:00 PM
Subject: Re: availability for a short contract with Health Canada

s.19(1)

Good Afternoon Erin,

Please accept the attached proposal for the work involved on this project. I
I have modified the proposed dates slightly, with the final deliverable due by
by May 11, 2012. I hope this is suitable. Please let me know if everything is in
is in order; I will then sign the proposal and email it to you.

Thank you,

Vlad

From: Erin Rutherford <erin.rutherford@hc-sc.gc.ca>
To: Vlad Kushnir [REDACTED]
Cc: Hanan Abramovici <hanan.abramovici@hc-sc.gc.ca>

000016

Sent: Thursday, March 22, 2012 3:22:11 PM

Subject: Re: availability for a short contract with Health Canada

Vlad,

Attached please find a statement of work for your review. Please don't hesitate to contact me if you have any questions.

If you are interested in taking on this project, please reply with a brief proposal.

[attachment "MDPV_ Draft Statement of Work.wpd" deleted by Erin Rutherford/HC-SC/GC/CA] (*See attached file: SOW MDPV_assessmentdraft.doc*)

Looking forward to hearing from you

Regards

Erin Rutherford

Manager/Gestionnaire

Drugs and Alcohol Research/Recherche, drogues et alcool

Office of Research and Surveillance / Bureau de la recherche et de la surveillance

Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au tabagisme

Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada / Santé Canada

123 Slater, MacDonald Building
Room A616 Address Locator: AL 3506 D
Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210
Fax: (613) 952-5188
E-mail: erin.rutherford@hc-sc.gc.ca

Vlad Kushnir ---2012-03-20 02:28:45 PM---Hello Erin, Thank you for contacting me with regards to this contract. I am interested in this under

From: Vlad Kushnir <[REDACTED]>
To: Erin Rutherford <erin.rutherford@hc-sc.gc.ca>
Cc: Hanan Abramovici <hanan.abramovici@hc-sc.gc.ca>
Date: 2012-03-20 02:28 PM

s.19(1)

000017

file://C:\WINDOWS\Temp\notesB955AA\~web4597.htm

Subject: **Re: availability for a short contract with Health Canada**

Hello Erin,

Thank you for contacting me with regards to this contract. I am interested in interested in this undertaking and would be delighted to get a more detailed detailed description of the requirements and work involved. I am also available available in the month of April, so with slight modifications to the proposed proposed timeline I believe the report can certainly be of high quality and completed on time. As per your convenience, we can set up a time to discuss discuss this project over the phone or please send me a statement of work and work and we will proceed from there.

Thank you; I look forward to hearing from you,

Vlad Kushnir

From: Erin Rutherford <erin.rutherford@hc-sc.gc.ca>

To: [REDACTED]

s.19(1)

Cc: Hanan Abramovici <hanan.abramovici@hc-sc.gc.ca>

Sent: Tuesday, March 20, 2012 9:05:26 AM

Subject: availability for a short contract with Health Canada

Good morning,

I was wondering about your availability for a short contract with Health Canada to review the literature on MDPV - pharmacology, abuse liability and addiction potential as part of the background for an issue analysis summary.

This work has just been proposed to us and it is a priority....

If you are available and interested, I would anticipate that we could have a contract ready to go by the end of next week with work to begin on April 3rd and wrap up around April 19th...these are just proposed timelines and we could certainly discuss further.

Looking forward to hearing from you

Regards

000018

file:///C:/WINDOWS/Temp/notesB955AA/~web4597.htm

Erin Rutherford

Manager/Gestionnaire

Drugs and Alcohol Research/Recherche, drogues et alcool

Office of Research and Surveillance / Bureau de la recherche et de la surveillance

Controlled Substances and Tobacco Directorate / Direction des substances
contrôlées et de la lutte au tabagisme

Healthy Environments and Consumer Safety Branch / Direction générale de la
santé environnementale et de la sécurité des consommateurs

Health Canada / Santé Canada

123 Slater, MacDonald Building

Room A616 Address Locator: AL 3506 D

Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210

Fax: (613) 952-5188

E-mail: erin.rutherford@hc-sc.gc.ca

[attachment "MDPV Assessment Proposal March 26, 2012.doc" deleted by
Erin Rutherford/HC-SC/GC/CA]

PROPOSAL (March 28, 2012)

March 28, 2012

Suzanne Desjardins, PhD
Director
Office of Drugs and Alcohol Research and Surveillance
Controlled Substances and Tobacco Directorate
Healthy Environments and Consumer Safety Branch
Health Canada
Tel: (613) 946-4223
Fax: (613) 948-7977
email: suzanne.desjardins@hc-sc.gc.ca

Dear Dr. Desjardins,

RE: MDPV Abuse Liability and Dependence Potential Assessment

I am writing this letter in confirmation that the stipulated contract requirements as specified by Health Canada will be fulfilled in their entirety.

The objectives of the project will be as follows:

1. Construct a report focusing on the abuse liability and dependence potential Methylenedioxypropylamphetamine (MDPV).
2. Review scientific literature and provide a summary of information concerning the chemistry, pharmacology, toxicology, abuse liability and dependence potential of MDPV. Information on MDPV pharmacology will include, if available, pharmacokinetics, pharmacodynamics of parent compound and active metabolites, biotransformation and elimination, and human and animal toxicology. Further, the report will provide scientific evidence of abuse liability and dependence potential from animal and human studies and will comment on overall abuse liability and addiction potential.

The above objectives will be completed in two phases:

1. A draft of the document pertaining to information on MDPV will be submitted to Health Canada for review by April 30, 2012, with the understanding that this timeline is based on a start date no later than April 10, 2012.
2. Following review of the draft document by Health Canada, any applicable feedback/ comments will be addressed and incorporated into the final version of the report. The final report on MDPV abuse liability and dependence potential will be submitted to Health Canada no later than May 11, 2012.

PROPOSAL (March 28, 2012)

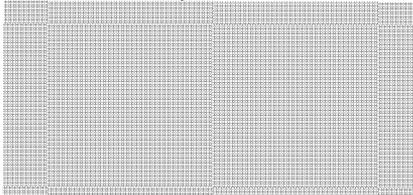
Please refer to the attached table for estimated completion dates for each deliverable/milestone.

I am very pleased and look forward to be working with Health Canada on this project. If you require anything further please do not hesitate to contact me.

Sincerely,



Vlad Kushnir, M.Sc.



s.19(1)

cc: Erin Rutherford
Manager, Drugs and Alcohol Research
Office of Research and Surveillance
Controlled Substances and Tobacco Directorate
Healthy Environments and Consumer Safety Branch
Health Canada
Tel: (613) 954-2210
Fax: (613) 952-5188
E-mail: erin.rutherford@hc-sc.gc.ca

PROPOSAL (March 28, 2012)

Deliverables/Milestones	Estimated Completion Date	Estimated Number of Hours	Rate/ hour	Cost
<p>1. Submit draft report summarizing scientific information pertaining to chemistry, pharmacology, toxicology, and abuse liability and potential of MDPV. The report will provide scientific evidence of abuse liability and dependence potential from animal and human studies and will comment on overall abuse liability and addiction potential</p>	30/04/2012	█	█	\$3750.00
HST (13%)				\$487.50
Subtotal				\$4237.50
<p>2. Revise draft document based on feedback from Health Canada and submit final report</p>	11/05/2012	█	█	\$1550.00
HST (13%)				\$201.50
Subtotal				\$1751.50
		TOTAL		\$5989.00

Statement of Work for Services

1.0 Scope

1.1 Title

Analysis of scientific information regarding the chemistry, pharmacology, toxicology, abuse liability and dependence potential of **Methylenedioxypropylvalerone (MDPV)** for use by the Office of Controlled Substances (OCS), Controlled Substances and Tobacco Directorate, Healthy Environments and Consumer Safety Branch (HECSB), Health Canada (HC).

1.2 Introduction

The Office of Controlled Substances (OCS) is currently examining how best to regulate MDPV. Increasing media attention and correspondence from the RCMP and Canada Border Services Agency led the OCS to consider the need to schedule MDPV. Currently, the OCS is preparing an Issue Analysis to determine if and how MDPV meet the factors considered when deciding to add substances to one of the Schedules to the CDSA.

1.3 Estimated Value

The total value of this contract shall not exceed \$6,000.00, including travel and living expenses and all applicable taxes.

1.4 Objectives of the Requirement

The net objective of this contract is the delivery of a paper summarizing the scientific information about the chemistry, pharmacology, toxicology, abuse liability and dependence potential of MDPV that will be used to guide the decision making of the appropriate scheduling of this substance.

1.5 Background, Assumptions and Specific Scope of the Requirement

Methylenedioxypropylvalerone (MDPV) has no history of approved medical use in Canada and is usually labelled "not for human consumption" on packaging. MDPV is the 3,4-methylenedioxy ring-substituted analogue of the compound Propylvalerone (a Schedule V controlled substance). MDPV has stimulant effects and is reported to have amphetamine-like or cocaine-type effects.

An increased appearance across Canada has prompted the need to determine whether this substance should be regulated as controlled substances under the Controlled Drugs and Substances Act (CDSA).

HC will use the final report to guide the decision making of the appropriate scheduling of

MDPV and in any documents required to support the scheduling decision.

2.0 Requirements

2.1 Tasks, Activities, Deliverables and Milestones

The tasks to be performed by the Contractor are as follows:

- review the scientific literature (scope is estimated to be less than 40 articles) and perform additional literature searches for new publications as necessary;
- draft the paper based on the outline and the available scientific information and submit to HC for review;
- review comments/ feedback provided by CSTD, and amend the draft paper as required;
- and
- submit a final paper, including an appropriate reference list, to HC.

Work is to be initiated on or about ***April 3, 2012*** and a draft paper to be available on or about ***April 19th***. The final paper is to be submitted to HC no later than ***April 30, 2012***.

2.2 Specifications and Standards

N/A.

2.3 Technical, Operational and Organizational Environment

The final report should be submitted in English in electronic format, either Word or Wordperfect.

2.4 Method and Source of Acceptance

The draft paper will be acceptable when it meets with the approval of the Director, ORS. The final paper must also meet with the approval of the Director, ORS.

2.5 Reporting Requirements

Although the Contractor will not be responsible for providing written progress reports, it is expected that the Contractor will be in regular communication with the Technical Authority and/or Departmental Representative in order to ensure that work on the paper is progressing in the required timelines.

2.6 Project Management Control Procedures

The Technical Authority and/or Departmental Representative shall arrange meetings between the Contractor and CSTD staff as required. The Technical Authority and/or Departmental Representative shall also ensure the appropriate distribution of the draft paper for comment within CSTD.

2.7 Change Management Procedures

Should changes to the timelines associated with this Contract be required, the Contractor shall inform the Technical Authority in writing of the intended changes. No changes however, will be made without the agreement of the Departmental Representative.

2.8 Ownership of Intellectual Property

The Crown will own the final paper produced by the Contractor.

3.0 Other Terms and Conditions of the SOW

3.1 Authorities

Departmental Representative:

Suzanne Desjardins, Ph.D
Director
Office of Research and Surveillance
Controlled Substances and Tobacco Directorate
Healthy Environments and Consumer Safety Branch
Health Canada
Tel: (613) 946-4223
Fax: (613) 952-5188
email: suzanne_desjardins@hc-sc.gc.ca

Technical Authority:

Erin Rutherford
Manager, Drugs and Alcohol Research
Office of Research and Surveillance
Controlled Substances and Tobacco Directorate
Healthy Environments and Consumer Safety Branch
Health Canada
Telephone: (613) 954-2210
Fax: (613) 952-5188
E-mail: erin.rutherford@hc-sc.gc.ca

Administrative/ Financial Contact:

Ann Scharf
Administrative Officer
Office of Management Services
Controlled Substances and Tobacco Directorate
Healthy Environments and Consumer Safety Branch
Health Canada
Tel: (613) 954-0152
Fax: (613) 954-2288
E-mail: ann.scharf@hc-sc.gc.ca

The Contractor shall obtain all direction for the work from either the Departmental Representative or the Technical Authority.

3.2 Health Canada Obligations

The Crown will provide the following:

- access to the Technical Authority, for the purposes of coordinating meetings, obtaining additional reference material; and
- comments on the draft paper within five (5) working days.

3.3 Contractor's Obligations

The Contractor will submit their final report in electronic format, either Word or Wordperfect.

3.4 Location of Work, Work site and Delivery Point

The work required from this contract will be carried out at the Contractor's regular place of business.

3.5 Language of Work

The paper is to be produced in English. Should Health Canada determine that translation is required for web posting purposes and/or for reference in its subsequent regulatory proposal, it will generate the required translation.

3.6 Special Requirements

N/A.

3.7 Security Requirements

N/A.

3.8 Insurance Requirements

N/A.

3.9 Travel and Living

N/A.

4.0 Project Schedule

4.1 Expected Start and Completion Dates

The services of the Contractor will be required for a period of approximately 4 weeks commencing on or about *April 3, 2012*. The expected completion date of this project is *April 30, 2012*.

4.2 Schedule and Estimated Level of Effort (Work Breakdown Structure)

The work will be done over the course of 4 weeks, with a draft report being provided to the Departmental Representative by *April 19th, 2012*, and the final report being provided no later than *April 30, 2012*.

5.0 Required Resources or Types of Roles to be Performed

The Contractor shall have a science education, and extensive experience reviewing and/or analyzing scientific information from peer-reviewed journals and other sources, for the purposes of preparing reports that may be subject to public scrutiny. In particular, the Contractor should have a sound knowledge of pharmacology, addiction and abuse liability.

In preparing the required paper, the Contractor should also be able to generate a draft paper that is clear and complete, and incorporate appropriate changes as per CSTD's comments, in order to generate a final paper that meets the required objectives.

6.0 Applicable Documents and Glossary

6.1 Applicable Documents

N/A.

6.2 Relevant Terms, Acronyms and Glossaries

N/A.

APPENDIX A: OUTLINE FOR PAPER ON MDPV

1. Purpose

To provide a scientific document to guide the scheduling assessment of MDPV under the CDSA. The resulting document will be used by HC in the scheduling decision and used in any necessary documentation to support a scheduling decision.

MDPV

1. Pharmacology
 - a. Pharmacokinetics
 - b. Pharmacodynamics
 - c. Biotransformation and elimination
 - d. Pharmacology of active metabolites
 - e. Human and animal toxicology

2. Scientific Evidence of Abuse Liability (excludes surveillance or epidemiological reports of abuse)
 - a. Animal studies
 - b. Human studies

3. Scientific Evidence of Addiction Potential
 - a. Animal studies
 - b. Human studies

Conclusion on overall abuse liability and addiction potential.

Re: Fw: MDPV Review - timing

Erin Rutherford to: Tara Phillips

Cc: Jocelyn Kula

2012-03-28 11:36 AM

Yes - the report will be available to OCS as of May 11th.

Thanks

Erin

Tara Phillips

Hi Erin, There is no issue with the final report be...

2012-03-28 11:35:08 AM

From: Tara Phillips/HC-SC/GC/CA
To: Erin Rutherford/HC-SC/GC/CA@HWC
Cc: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-03-28 11:35 AM
Subject: Re: Fw: MDPV Review - timing

Hi Erin,

There is no issue with the final report being delivered by May 11, 2012, in terms of the current workplan.

I am assuming that the report would be ready to use in terms of drafting the Issue Analysis Summary and other documentation as of May 11, 2012. If there is any time required by ORS for additional review following receipt of the final report, please advise. I am relatively new to OCS and just want to make sure I understand the process and steps correctly.

Thank you,

Tara
946-6521

----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2012-03-28 10:31 AM -----

From: Erin Rutherford/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Cc: Suzanne Desjardins/HC-SC/GC/CA@HWC, Hanan Abramovici/HC-SC/GC/CA@HWC
Date: 2012-03-26 03:11 PM
Subject: MDPV Review - timing

Jocelyn,

We have just heard from our proposed contractor that due to another project, the earliest that he could provide a final report on MDPV would be May 11th.

Would that be workable with your timelines? We could look for another contractor if the timing is a deal breaker for you but our preference would be to delay the final report and use a contractor that has produced excellent work in the past.

If you are OK with the May 11th deliverable, we can get the contract in place this week.

Thanks

Erin

Erin Rutherford

Manager/Gestionnaire

Drugs and Alcohol Research/Recherche, drogues et alcool

Office of Research and Surveillance / Bureau de la recherche et de la surveillance

Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au
tabagisme

Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et
de la sécurité des consommateurs

Health Canada / Santé Canada

123 Slater, MacDonald Building

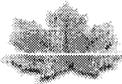
Room A616 Address Locator: AL 3506 D

Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210

Fax: (613) 952-5188

E-mail: erin.rutherford@hc-sc.gc.ca



Re: Draft MDPV Assessment 
Hanan Abramovici to: Erin Rutherford

2012-04-30 01:42 PM

OK. No problem.
Thanks,
H.

Erin Rutherford Thanks Hanan, I would like to have your comme... 2012-04-30 01:41:05 PM

From: Erin Rutherford/HC-SC/GC/CA
To: Hanan Abramovici/HC-SC/GC/CA@HWC
Date: 2012-04-30 01:41 PM
Subject: Re: Draft MDPV Assessment

Thanks Hanan,

I would like to have your comments by end of day on Wednesday. We'll then provide our comment to Suzanne for her to approve, so that Vlad can have the final comments by end of day Friday.

I will also be providing the draft to OCS for their comments as well.

Thanks

Erin

Hanan Abramovici Hi Erin, I will review and provide comments. Wh... 2012-04-30 01:35:01 PM

From: Hanan Abramovici/HC-SC/GC/CA
To: Erin Rutherford/HC-SC/GC/CA@HWC
Date: 2012-04-30 01:35 PM
Subject: Re: Draft MDPV Assessment

Hi Erin,
I will review and provide comments. When should we aim for? End of next week?
Thanks,
Hanan

Erin Rutherford Thank you very much. We will review the draft r... 2012-04-30 01:33:07 PM

From: Erin Rutherford/HC-SC/GC/CA **s.19(1)**
To: Vlad Kushnir - 
Cc: Hanan Abramovici <hanan.abramovici@hc-sc.gc.ca>
Date: 2012-04-30 01:33 PM
Subject: Re: Draft MDPV Assessment

Thank you very much. We will review the draft report and provide comments soon.

Regards

Erin Rutherford

Manager/Gestionnaire
Drugs and Alcohol Research/Recherche, drogues et alcool
Office of Research and Surveillance / Bureau de la recherche et de la surveillance
Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au
tabagisme
Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et
de la sécurité des consommateurs
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Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210
Fax: (613) 952-5188
E-mail: erin.rutherford@hc-sc.gc.ca

Vlad Kushnir Good Day Erin, Please accept the attached draft... 2012-04-30 12:53:44 PM

From: Vlad Kushnir <[REDACTED]> **s.19(1)**
To: Erin Rutherford <erin.rutherford@hc-sc.gc.ca>
Cc: Hanan Abramovici <hanan.abramovici@hc-sc.gc.ca>
Date: 2012-04-30 12:53 PM
Subject: Draft MDPV Assessment

Good Day Erin,
Please accept the attached draft report on MDPV abuse liability and dependence potential.
I look forward to your feedback. Best regards,
Vlad Kushnir[attachment "MDPV Assessment DRAFT.doc" deleted by Erin
Rutherford/HC-SC/GC/CA]

**3,4-Methylenedioxypropylamphetamine (MDPV) Abuse Liability and Dependence
Potential Assessment**

Prepared by Vlad Kushnir, MSc
April 30, 2012

3,4-Methylenedioxypropylone (MDPV) Abuse Liability and Dependence Potential Assessment

Background

The synthetic cathinone 3,4-Methylenedioxypropylone, also known as MDPV, is a designer drug that is used for its cocaine and amphetamine-like psychoactive effects. First synthesized and patented by Boehringer Ingelheim in 1969,¹ it has only recently gained exposure among recreational drug users. It is one of a number synthetic cathinones that are derivatives of the vegetable cathinone, a naturally occurring beta-ketone amphetamine analogue found in the leaves of *Catha edulis* (khat). Considered as “legal highs”, synthetic cathinones are generally sold as “bath salts” or “plant food” and labelled “not for human consumption” to circumvent regulatory control and drug abuse legislation. MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities. The substance does not have any known medical uses and is an analogue of the compound propylone (a Schedule V controlled substance).

Chemistry

Chemical Structure

The compound 3,4-Methylenedioxypropylone (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5yl)-2-pyrrolidin-1-yl-pentan-1-one) is a pyrrolidine derivative of the synthetic cathinone propylone, differing in the presence of a 3,4-methylenedioxy group linked to the aromatic ring.¹ Its molecular formula is C₁₆H₂₁NO₃ and has a molecular weight of 275.34284 g/mol; Chemical Abstract Service Number 687603-66-3. MDPV is a solid at room temperature and has a melting point of 209.3 °C and a boiling point of 476 °C. It is available as an amorphous solid or crystalline powder that varies in colour, depending on composition and added impurities. In the free base form it is brown or yellowish green, whereas as a hydrochloride salt it is white in appearance.

Pharmacology

Biotransformation

The metabolism of MDPV has been evaluated only *in vitro* in two studies. Examination of MDPV metabolism in human liver cells has prompted the proposal of a metabolic pathway that involves first, the opening of the methylenedioxy ring, followed by demethylation that gives rise to a catechol ring, which is in turn methylated by catecholmethyltransferase.² The aromatic pyrrolidine ring and side chain are subsequently hydroxylated, followed by oxidation to the corresponding lactam, as well as ring opening to the corresponding carboxylic acid. It was documented that the demethylation step of the Phase I metabolism, in particular, is catalyzed

through CYP450 isozymes 2C19, 2D6 and 1A2.³ Approximately 80% of MDPV remains unmetabolized, 10% is metabolized into cetechol pyrovalerone, and 7% is metabolized into methylcatechol pyrovalerone. The high percentage of the parent compound was postulated to remain as a result of very high concentrations of MDPV added to liver microsome samples. Nevertheless, it was determined that the main metabolites further undergo Phase II glucoronidation and sulfation transformations to allow for renal excretion.²

Elimination

The excretion profile of MDPV and its metabolites has not been studied in animals or humans. However, several reports have documented MDPV concentrations in urine samples obtained from patients presenting to hospital and poison centres, as well as opioid dependent patients undergoing opioid substitution treatment. MDPV concentrations in urine have been noted to range from 0.034 – 3.9 mg/L in those cases.⁴⁻⁶ While anecdotal reports indicate that users ingest anywhere between 5 – 30mg of MDPV per single session,⁶⁻⁸ variable dose intake among users and undocumented time since ingestion prohibit from determining the MDPV elimination half-life and concentration of excreted metabolites.

Pharmacological Mechanism of Action

The exact mechanism of action of MDPV has not been fully elucidated, with only a handful of studies investigating its neurobiological effects. *In-vitro*, MDPV has demonstrated to act as a potent dopamine ($IC_{50} = 52.0 \pm 20$ nM) and norepinephrine ($IC_{50} = 28.3 \pm 8.1$ nM) reuptake inhibitor, exhibiting dopamine and norepinephrine reuptake inhibition 9 and 13 times greater than cocaine, respectively. In contrast, inhibition of serotonin reuptake was found to be markedly less pronounced ($IC_{50} = 2780 \pm 590$ nM), a finding that reflected in the reduced binding affinity for the serotonergic transporter.⁹ Microdialysis studies in freely moving mice supported the *in-vitro* findings, showing that 60 minutes following oral administration of MDPV, extracellular striatal dopamine content was 2.1 times higher in the experimental group compared to those in the control group. While substantial, MDPV induced increases in dopamine levels, however, were milder than those produced by the amphetamine-like stimulants methamphetamine and methylenedioxymethamphetamine (MDMA). Further, serotonin concentrations were not significantly influenced by MDPV administration.^{10, 11}

Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. MDPV binding affinities at the dopamine transporter ($K_i = 21.4 \pm 4.6$ nM) and norepinephrine transporter ($K_i = 195 \pm 26$ nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively. Binding affinity for the serotonin transporter was considerably lower ($K_i = 3770 \pm 560$ nM), indicating that MDPV is relatively inactive at this site.⁹

Human Toxicology

At present, a toxicological profile for MDPV, including a dose-response relationship and the median lethal dose (LD₅₀), has not yet been established. Primary indication of MDPV toxicity in the scientific community has developed from case reports documenting individuals presenting to hospital emergency departments after intake of “bath salts”. The most common symptoms of acute toxicity involve those associated with cardiovascular, neurological, and psychopathological function. Specifically, they include: tachycardia, chest pain, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, delusions, auditory and visual hallucinations, paranoid psychosis, agitation, aggression, anxiety, panic attacks, insomnia, memory loss, hyperthermia, rhabdomyolysis, abdominal pain, decreased appetite, vomiting, and kidney dysfunction.^{4, 12-17} Some effects such as sleeping difficulties, anxiety and agitation have been reported to persist for more than one day following ingestion,¹³ while others have been suggested to continue for as long as a week.¹⁵ Several cases of drug-induced delirium and even death have also been noted, where MDPV was the sole intoxicant.^{14, 17} Most commonly, however, as MDPV is co-ingested with other substances, including benzodiazepines, amphetamines, cannabis, and ethanol,^{5, 18} it is unclear whether the list of acute toxic effects is purely a result of MDPV or a combination of drug-drug interactions.

Evidence of Abuse Liability

Animal or human laboratory studies on abuse liability of MDPV have not been carried out. Specifically, the most common approaches used to investigate abuse potential of drugs in animals, namely, self-administration tests, conditioned place preference, drug discrimination, and psychomotor tests are not documented in the scientific literature. Similarly, abuse liability trials in recreational drug users using double blind, randomized, double dummy, placebo or positive comparator controlled, or crossover designs have not been conducted. Only one study has made an inference to MDPV being liable to abuse. Through the use of the gas chromatography-mass spectrometry procedure to detect MDPV and other substances in urine of opioid-dependent patients undergoing opioid substitution treatment, the authors suggested that MDPV is mainly used a “non-detectable” substitute for amphetamine primarily to increase concentration among users. Moreover, they emphasized that the inability to detect MDPV through conventional immunoassay drug screenings is a notable factor that may contribute to the drug’s misuse.⁶

The numerous case reports of acute MDPV intoxication highlighted in the scientific literature may be in their own respect, an indirect indication that the drug may possess abuse potential. Among recreational drug users, MDPV may be gaining popularity specifically for its anecdotal desired subjective effects. Synthesizing internet information on the effects of MDPV, one review has noted that specifically at low doses (undefined), MDPV is used to increase concentration, the capacity to work, and sexual performance. Other desired psychotomimetic effects include increased sociability, energy, limited euphoria, and mild empathogenic effects.⁷

Evidence of Physical Dependence

Behavioural animal data on the reinforcing and physical dependence-producing effects of MDPV is not available. Clinical trials on MDPV abuse liability have also not been conducted, therefore scientific evidence of tolerance or withdrawal, which is critical to the definition of physical dependence, has not been observed. Although one literature source cited the “development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV”,⁷ these drug-related effects could not be confirmed.

Evidence of possible physical dependence and tolerance building effects is indirect and can only be gleaned from case studies and unverified internet information reported by users. Penders and Gestring¹⁴ reported of a woman admitted to the psychiatric unit of a community hospital by way of an involuntary commitment initiated by her husband. The individual experienced fearful hallucinations of a home invasion that precipitated following daily use of MDPV for 2 weeks prior to admission. It is possible to infer that repeated and perhaps uncontrollable use of the drug is suggestive of physical dependence-like effects, however, this conclusion is highly speculative. Indication of possible tolerance is based on internet discussions documenting common redosing in a single session as well as using doses of over 200mg.⁷ Although MDPV is reported to have a short duration of action, use of doses well over 6 times the typical 5 to 30 mg used in a single ingestion, suggests that users may develop tolerance to the drug's effects and thus possible physical dependence.

Conclusions

The abuse potential assessment of a drug should be based on a composite analysis of chemistry, pharmacology, clinical data, health risks that the drug presents, as well as ease of access to the drug and administration. The limited pharmacological data suggests that MDPV is similar to other synthetic cathinones, inhibiting reuptake and stimulating the release of dopamine and norepinephrine. This mechanism of action has been associated with the production of amphetamine-like effects and is supported by user reports of stimulant and mild psychoactive effects similar to those of amphetamine and MDMA. Further, as the drug's chemical structure allows it to be highly soluble and thus more easily cross the blood-brain barrier, a similar abuse liability profile to amphetamine may be expected. Taken together with the ease with which “bath salts” can be purchased, numerous routes of administration and unconfirmed user accounts of short duration of action, there may be preliminary indication that MDPV is likely to be abused. However, in the absence of clinical studies, by relying solely on sparse pharmacological data and indirect evidence suggestive of abuse liability, it is not possible to make a definitive statement of abuse liability.

At present, there is no focused research on the dependence potential of MDPV and other synthetic cathinones. While dopaminergic properties, particularly in the mesocorticolimbic system, might be considered a signal suggesting the presence of reinforcing properties, sound scientific evidence that MDPV possesses dependence potential is not available. Therefore, it is not possible to conclude whether MDPV does or does not have dependence potential.

References

1. Yohannan JC, Bozenko JS. The characterization of 3,4-methylenedioxypropylvalerone. *Microgram Journal*. 2010;7:12-5.
2. Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom*. 2010;24(18):2706-14.
3. Meyer MR, Du P, Schuster F, Maurer HH. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-propylvalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom*. 2010;45(12):1426-42.
4. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin Syndrome Associated With MDPV Use: A Case Report. *Ann Emerg Med*. 2011.
5. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila)*. 2011;49(6):499-505.
6. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit*. 2011;33(2):257-63.
7. Coppola M, Mondola R. 3,4-methylenedioxypropylvalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett*. 2012;208(1):12-5.
8. Drug & Chemical Evaluation Section. 3,4-Methylenedioxypropylvalerone (MDPV). US Drug Enforcement Administration, Control OoD; 2011.
9. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Propylvalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem*. 2006;49(4):1420-32.
10. Fuwa T., Fukumori N., Tanaka T., Kubo Y., Ogata A., Uehara S., et al. Microdialysis study of drug effects on central nervous system. Changes in dopamine levels in mice striatum after oral administration of methylenedioxypropylvalerone [in Japanese]. *Tokyo-to Kenko Anzen Kenkyu Senta Kenkyu Nenpo*. 2007;58:287-92.
11. Fuwa T., Kodama T., Honda Y., Tanaka T., Kubo Y., Ohashi N., et al. Influence of Methylenedioxypropylvalerone on Central Nervous System - Using Microdialysis Methods [in Japanese]. *ChemBio*. 2009;5:62-72.
12. Centre for Disease Control and Prevention (CDC). Emergency department visits after the use of a drug sold as "bath salts". Michigan: 2011.
13. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, et al. Energy-1 ('NRG-1'): don't believe what the newspapers say about it being legal. *Emerg Med J*. 2011;28(12):1068-70.

14. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: "Bath Salts". *Gen Hosp Psychiatry*. 2011;33(5):525-6.
15. Durham M. Ivory wave: the next mephedrone? *Emerg Med J*. 2011;28(12):1059-60.
16. Borek HA, Holstege CP. Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypyrovalerone. *Ann Emerg Med*. 2012.
17. Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypyrovalerone (MDPV). *J Med Toxicol*. 2012;8(1):69-75.
18. Kriikku P, Wilhelm L, Schwarz O, Rintatalo J. New designer drug of abuse: 3,4-Methylenedioxypyrovalerone (MDPV). Findings from apprehended drivers in Finland. *Forensic Sci Int*. 2011;210(1-3):195-200.

Draft MDPV assessment

Erin Rutherford to: Suzanne Desjardins

2012-04-30 01:46 PM

Suzanne,

Attached below is the draft MDPV assessment from Vlad.

Hanan is reviewing and we will provide you with his comments by end of day Wednesday. In addition, I have sent a copy to Jocelyn for her review and comments by end of day Wednesday.

On Thursday morning, I will provide you with Hanan and Jocelyn's comments for your review and approval. We would like to have final comments ready to send to Vlad by end of day Friday.

Thanks

Erin



MDPV Assessment DRAFT.doc



Comments on MDPV report
Hanan Abramovici to: Erin Rutherford

2012-04-30 03:14 PM

Hi Erin,
Please find my comments on Vlad's MDPV report.
Thanks,
Hanan



MDPV Assessment DRAFT_HA comments.doc

3,4-Methylenedioxyprovalerone (MDPV) Abuse Liability and Dependence Potential Assessment

Prepared by Vlad Kushnir, MSc
April 30, 2012

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3,4-Methylenedioxypropylvalerone (MDPV) Abuse Liability and Dependence Potential Assessment

Background

The synthetic cathinone 3,4-Methylenedioxypropylvalerone, also known as MDPV, is a designer drug that is used for its ~~cocaine and amphetamine~~ stimulant-like psychoactive effects (reference?). First synthesized and patented by Boehringer Ingelheim in 1969,¹ it has only recently gained exposure among recreational drug users. It is one of a number synthetic cathinones that are derivatives of the vegetable cathinone, a naturally occurring beta-ketone amphetamine analogue found in the leaves of *Catha edulis* (khat) (reference?). ~~Considered as "legal highs",~~ Synthetic cathinones are generally sold as "bath salts" or "plant food" and labelled "not for human consumption" to circumvent regulatory control and drug abuse legislation. As such, they are considered "legal highs". MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities including(and provide references). The substance does not have any known medical uses and is an analogue of the compound propylvalerone (a Schedule V controlled substance).

Chemistry

Chemical Structure

The compound 3,4-Methylenedioxypropylvalerone (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5yl)-2-pyrrolidin-1-yl-pentan-1-one) is a pyrrolidine derivative of the synthetic cathinone propylvalerone, differing in the presence of a 3,4-methylenedioxy group linked to the aromatic ring.¹ Its molecular formula is C₁₆H₂₁NO₃ and it has a molecular weight of 275.34284 g/mol; Chemical Abstract Service Number 687603-66-3. MDPV is a solid at room temperature and has a melting point of 209.3 °C and a boiling point of 476 °C (reference?). It is available as an amorphous solid or crystalline powder that varies in colour, depending on composition and added impurities (reference). In the free base form it is brown or yellowish green, whereas as a hydrochloride salt it is white in appearance (reference).

Pharmacology

Biotransformation

Very little information is available regarding the biotransformation of MDPV and what little is known comes from only two *in vitro* studies. The metabolism of MDPV has been evaluated only *in vitro* in two studies (references). Examination of MDPV metabolism in human liver cells (intact cells? microsomes?) has prompted the proposal of a metabolic pathway that involves first, the opening of the methylenedioxy ring, followed by demethylation that gives rise to a catechol ring, which is in turn methylated by catecholmethyltransferase.² The aromatic

Comment [HABR1]: Perhaps we should just stick to biotransformation or metabolism but not use both to ensure we are consistent in our terminology?

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pyrrolidine ring and side chain are subsequently hydroxylated, followed by oxidation to the corresponding lactam, as well as ring opening to the corresponding carboxylic acid. It was documented that the demethylation step of the Phase I metabolism, in particular, is catalyzed through CYP450 isozymes 2C19, 2D6 and 1A2.³ Approximately 80% of MDPV remains unmetabolized, 10% is metabolized into caetechol pyrovalerone, and 7% is metabolized into methylcatechol pyrovalerone. The high percentage of unmetabolized ~~the~~ parent compound was postulated to ~~remain as a result of~~ from the very high concentrations of MDPV added to liver microsome samples. Nevertheless, it was determined that the main metabolites further undergo Phase II glucueronidation and sulfation transformations to allow for renal excretion.²

Elimination

The excretion profile of MDPV and its metabolites has not been studied in animals or humans. However, several reports have documented MDPV concentrations in urine samples obtained from patients presenting to hospital and poison centres, as well as opioid dependent patients undergoing opioid substitution treatment. MDPV concentrations in urine have been noted to range from 0.034 – 3.9 mg/L in those cases.⁴⁻⁶ While anecdotal reports indicate that users ingest anywhere between 5 – 30mg of MDPV per single session,⁶⁻⁸ variable dose intake among users and undocumented time since ingestion prohibit from determining the MDPV elimination half-life and concentration of excreted metabolites.

Pharmacological Mechanism of Action

The exact mechanism of action of MDPV has not been fully elucidated, with only a handful of studies investigating its neurobiological effects (references?). In-vitro, MDPV has demonstrated to act as a potent dopamine ($IC_{50} = 52.0 \pm 20$ nM) and norepinephrine ($IC_{50} = 28.3 \pm 8.1$ nM) reuptake inhibitor, exhibiting dopamine and norepinephrine reuptake inhibition 9 and 13 times greater than cocaine, respectively (references?). In contrast, inhibition of serotonin reuptake was found to be markedly less pronounced ($IC_{50} = 2780 \pm 590$ nM), a finding supported by that reflected in the observed reduced binding affinity for the serotonergic transporter.⁹ Microdialysis studies in freely moving mice supported some of the in-vitro findings, showing that 60 minutes following oral administration of MDPV, extracellular striatum dopamine content was 2.1 times higher in the experimental group compared to those in the control group (references?). While substantially significant, the MDPV-induced increases in dopamine levels; however, were milder than those produced by the amphetamine-like stimulants methamphetamine and methylenedioxymethamphetamine (MDMA) (references?). Further, serotonin concentrations were not significantly influenced by MDPV administration.^{10, 11}

Comment [HABR2]: Can you add a bit more information on the exact in vitro model used here? Were they synaptosomes?

Comment [HABR3]: I added "some" because the studies supported the dopamine observations but no information was provided for norepinephrine.

Comment [HABR4]: How much milder?

Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. MDPV binding affinities at the dopamine transporter ($K_i = 21.4 \pm 4.6$ nM) and norepinephrine transporter ($K_i = 195 \pm 26$ nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively (references?). Binding affinity for the serotonin transporter was considerably lower ($K_i = 3770 \pm 560$ nM), indicating that MDPV is relatively inactive at this site.⁹

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Human Toxicology

At present, a toxicological profile for MDPV, including a dose-response relationship and the median lethal dose (LD₅₀), has not yet been established. Primary indication of MDPV toxicity in the scientific community has developed—derives from case reports documenting individuals presenting to hospital emergency departments after intake of “bath salts”. The most common symptoms of acute toxicity involve those associated with cardiovascular, neurological, and psychopathological function. Specifically, these symptoms include: tachycardia, chest pain, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, delusions, auditory and visual hallucinations, paranoid psychosis, agitation, aggression, anxiety, panic attacks, insomnia, memory loss, hyperthermia, rhabdomyolysis, abdominal pain, decreased appetite, vomiting, and kidney dysfunction.^{4, 12-17} Some effects such as sleeping difficulties, anxiety and agitation have been reported to persist for more than one day following ingestion,¹³ while others have been suggested to continue for as long as a week.¹⁵ Several cases of drug-induced delirium and even death have also been noted, where MDPV was the sole intoxicant.^{14, 17} Most commonly, however, as MDPV is typically (often?) co-ingested with other substances, including benzodiazepines, amphetamines, cannabis, and ethanol,^{5, 18} it is unclear whether the list of acute toxic effects is purely a result of MDPV or a combination of drug-drug interactions.

Evidence of Abuse Liability

Animal or human laboratory studies on abuse liability of MDPV have not been carried out. Specifically, the most common approaches used to investigate abuse potential of drugs in animals, namely, self-administration tests, conditioned place-preference, drug discrimination, and psychomotor tests are not documented in the scientific literature. Similarly, abuse liability trials—studies in recreational drug users using double-blind, randomized, double-dummy, placebo or positive comparator controlled, or crossover designs have not been conducted. Only one study has made an inference to MDPV being liable to abuse (reference?). Through the use of the gas chromatography-mass spectrometry procedure to detect MDPV and other substances in urine of opioid-dependent patients undergoing opioid substitution treatment, the authors suggested that MDPV is mainly used as a “non-detectable” substitute for amphetamine primarily to increase concentration among users (reference). Moreover, the authors emphasized that the inability to detect MDPV through conventional immunoassay drug screenings is a notable factor that may contribute to the drug’s misuse.⁶

The numerous case reports of acute MDPV intoxication highlighted in the scientific literature may be in their own respect, an indirect indication that the drug may possess abuse potential. Among recreational drug users, it appears that MDPV may be gaining popularity specifically for its anecdotally-described desirable subjective psychotropic effects. Synthesizing internet information on the effects of MDPV, one literature review has noted that specifically at low doses (undefined), MDPV is used to increase concentration, the capacity to

Comment [HABR5]: Was this self-reported by the users?

Comment [HABR6]: I think misuse in this context would suggest that MDPV has actual therapeutic utility. I think “abuse” would be a more appropriate term here??

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work, and sexual performance (reference?). Other desired psychotomimetic effects include increased sociability, energy, limited euphoria, and mild empathogenic effects.⁷

Evidence of Physical Dependence

Behavioural animal data on the reinforcing and physical dependence-producing effects of MDPV is not available. Clinical trials on MDPV abuse liability have also not been conducted, therefore scientific evidence of tolerance or withdrawal, which is critical to the definition of physical dependence, has not been observed. Although one literature source cited the “development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV”,⁷ these drug-related effects could not be confirmed.

Evidence of possible physical dependence and tolerance building effects is indirect and can only be gleaned from case studies and unverified internet information reported by users. Penders and Gestring¹⁴ reported of a woman admitted to the psychiatric unit of a community hospital by way of an involuntary commitment initiated by her husband. The individual experienced fearful hallucinations of a home invasion that precipitated following daily use of MDPV for 2 weeks prior to admission. It is possible to infer that repeated and perhaps uncontrollable use of the drug is suggestive of physical dependence-like effects, however, this conclusion is highly speculative. Indication of possible tolerance is based on internet discussions documenting common redosing in a single session as well as using doses of over 200mg.⁷ Although MDPV is reported to have a short duration of action, use of doses well over 6 times the typical 5 to 30 mg used in a single ingestion, suggests that users may develop tolerance to the drug's effects and thus possible physical dependence.

Conclusions

The abuse potential assessment of a drug should be based on a composite analysis of chemistry, pharmacology, clinical data, health risks that the drug presents, as well as ease of access to the drug and administration. The limited pharmacological data suggests that MDPV is similar to other synthetic cathinones, inhibiting reuptake and stimulating the release of dopamine and norepinephrine. This mechanism of action has been associated with the production of amphetamine-like effects and is supported by user reports of stimulant and mild psychoactive effects similar to those of amphetamine and MDMA. Further, as the drug's chemical structure allows it to be highly soluble and thus more easily cross the blood-brain barrier, a similar abuse liability profile to amphetamine may be expected. Taken together with the ease with which “bath salts” can be purchased, numerous routes of administration and unconfirmed user accounts of short duration of action, there may be preliminary indication that MDPV is likely to be abused. However, in the absence of clinical studies, by relying solely on sparse pharmacological data and indirect evidence suggestive of abuse liability, it is not possible to make a definitive statement of abuse liability.

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At present, there is no focused research on the dependence potential of MDPV and other synthetic cathinones. While dopaminergic properties, particularly in the mesocorticolimbic system, might be considered a signal suggesting the presence of reinforcing properties, sound scientific evidence that MDPV possesses dependence potential is not available. Therefore, it is not possible to conclude whether MDPV does or does not have dependence potential.

Comment [HABR7]: I would remove this sentence here as it adds new information that was not provided earlier in the text. Otherwise, it could be moved into the text at an earlier point and expanded upon.

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References

1. Yohannan JC, Bozenko JS. The characterization of 3,4-methylenedioxypropylone. *Microgram Journal*. 2010;7:12-5.
2. Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom*. 2010;24(18):2706-14.
3. Meyer MR, Du P, Schuster F, Maurer HH. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-propylone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom*. 2010;45(12):1426-42.
4. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin Syndrome Associated With MDPV Use: A Case Report. *Ann Emerg Med*. 2011.
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6. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit*. 2011;33(2):257-63.
7. Coppola M, Mondola R. 3,4-methylenedioxypropylone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett*. 2012;208(1):12-5.
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9. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem*. 2006;49(4):1420-32.
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12. Centre for Disease Control and Prevention (CDC). Emergency department visits after the use of a drug sold as "bath salts". Michigan: 2011.
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Re: Draft MDPV assessment for comments 

Erin Rutherford to Jocelyn Kula

cc: Tara Phillips

2012-05-01 10:47 AM

Please see attached.

Thanks

Erin



SOW MDPV_assesmentfinal.doc

Jocelyn Kula

Hi Erin We are reviewing the report and hope to...

2012-05-01 10:29:17 AM

From: Jocelyn Kula/HC-SC/GC/CA
To: Erin Rutherford/HC-SC/GC/CA@HWC
Cc: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-01 10:29 AM
Subject: Re: Draft MDPV assessment for comments

Hi Erin

We are reviewing the report and hope to have some feedback for you tomorrow. In the interim, would it be possible to get a copy of the SoW for the contract, just so that we make sure our comments reflect what Mr Kushnir was asked to do.

Thanks
Jocelyn

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire

Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada/ Santé Canada

Tel: (613) 946-0125 Fax: (613) 946-4224

Erin Rutherford

Attached please find a draft MDPV assessment...

2012-04-30 01:43:51 PM

From: Erin Rutherford/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-04-30 01:43 PM
Subject: Draft MDPV assessment for comments

Attached please find a draft MDPV assessment for your review and comments.
[attachment "MDPV Assessment DRAFT.doc" deleted by Jocelyn Kula/HC-SC/GC/CA]

I would appreciate if you could provide me with any comments prior to COB Wednesday.

Regards



Re: Fw: Comments on MDPV report 
Vincent Marleau to: Erin Rutherford

2012-05-01 12:44 PM

Hi Erin,

Here are my corrections and comments for this report:



MDPV Assessment DRAFT_VM comments.doc

It was pretty good albeit not conclusive because of lack of evidence. I don't quite know the use of this document but I would like to see more links to the CDSA and other rulings by other states. Hanan pointed out the lack of references but otherwise it was simple and clear.

If you would like to chat about my comments or concerns, please do not hesitate,

Kind regards,

Vincent Marleau
FSWEP Student | Étudiant FSWEP
Junior Scientific Analyst | Analyste Scientifique Junior
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
environnementale et de la sécurité des consommateurs (DGSESC)
Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
vincent.marleau@hc-sc.gc.ca
Telephone | Téléphone 613-946-3591
Government of Canada | Gouvernement du Canada

Erin Rutherford

Vincent, I know your top priority is the ATI, but I...

2012-05-01 09:54:42 AM

From: Erin Rutherford/HC-SC/GC/CA
To: Vincent Marleau/HC-SC/GC/CA@HWC
Cc: Evelyn Soo/HC-SC/GC/CA@HWC
Date: 2012-05-01 09:54 AM
Subject: Fw: Comments on MDPV report

Vincent,

I know your top priority is the ATI, but I know you have an interest in the drug issues, so this is just for your information.

Here is the draft report, with Hanan's comments included.

If you have any additional comments or suggestions, please let me know by end of day Wednesday May 2nd.

Thanks

Erin

Erin Rutherford

Manager/Gestionnaire

Drugs and Alcohol Research/Recherche, drogues et alcool

Office of Research and Surveillance / Bureau de la recherche et de la surveillance

Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au
tabagisme

Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et
de la sécurité des consommateurs

Health Canada / Santé Canada

123 Slater, MacDonald Building

Room A616 Address Locator: AL 3506 D

Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210

Fax: (613) 952-5188

E-mail: erin.rutherford@hc-sc.gc.ca

----- Forwarded by Erin Rutherford/HC-SC/GC/CA on 2012-05-01 09:49 AM -----

From: Hanan Abramovici/HC-SC/GC/CA
To: Erin Rutherford/HC-SC/GC/CA@HWC
Date: 2012-04-30 03:14 PM
Subject: Comments on MDPV report

Hi Erin,
Please find my comments on Vlad's MDPV report.
Thanks,
Hanan

[attachment "MDPV Assessment DRAFT_HA comments.doc" deleted by Vincent Marleau/HC-SC/GC/CA]

3,4-Methylenedioxypropylvalerone (MDPV)
Abuse Liability and Dependence Potential Assessment

Prepared by Vlad Kushnir, MSc
April 30, 2012

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3,4-Methylenedioxypropylone (MDPV) Abuse Liability and Dependence Potential Assessment

Background

The synthetic cathinone 3,4-Methylenedioxypropylone, also known as MDPV, is a designer drug that is used for its stimulant-like psychoactive effects (reference?). First synthesized and patented by Boehringer Ingelheim in 1969,¹ it has only recently gained exposure among recreational drug users. It is one of a number of synthetic cathinones that are derivatives of cathinone, a naturally occurring beta-ketone amphetamine analogue found in the leaves of *Catha edulis* (khat) (reference?). Synthetic cathinones are generally sold as “bath salts” or “plant food” and labelled “not for human consumption” to circumvent regulatory control and drug abuse legislation. As such, they are considered “legal highs”. MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities including ... (and provide references). The substance does not have any known medical uses and is an analogue of the compound propylone (controlled under Item 26 of Schedule IV, to the CDSA).

Comment [V1]: It would be good to see the status of this substance in different countries... Like it is temporarily controlled under Schedule I of the CSA in the U.S. - http://www.deadiversion.usdoj.gov/drugs_concern/mdpv.pdf

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Comment [V2]: The U.S. considers it similar in structure to MDMA (Sub-Item 1(9) of Schedule III to the CDSA) and MDEA (N-ethyl-alpha-methyl-1,3-benzodioxole-5-ethanamine, Sub-Item 1(13) of Schedule III to the CDSA). These rulings give you more support and the analogue ruling could apply as well...

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Chemistry

Chemical Structure

The compound 3,4-Methylenedioxypropylone (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-yl-pentan-1-one) is a pyrrolidine derivative of the synthetic cathinone propylone (reference?), differing in the presence of a 3,4-methylenedioxy group linked to the aromatic ring instead of a methyl.¹ Its molecular formula is C₁₆H₂₁NO₃ and it has a molecular weight of 275.34284 g/mol; Chemical Abstract Service Number 687603-66-3. MDPV is a solid at room temperature and has a melting point of 209.3 °C and a boiling point of 476 °C (reference?). It is available as an amorphous solid or crystalline powder that varies in colour (from white to light yellow ... reference?), depending on composition and added impurities (reference). In the free base form it is brown or yellowish green, whereas as a hydrochloride salt it is white in appearance (reference).

Comment [HABR3]: Perhaps we should just stick to biotransformation or metabolism but not use both to ensure we are consistent in our terminology?

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Pharmacology

Biotransformation

Very little information is available regarding the biotransformation of MDPV and what little is known comes from only two *in vitro* studies (references). Examination of MDPV metabolism in human liver cells (intact cells? microsomes?) has prompted the proposal of a metabolic pathway that involves first, the opening of the methylenedioxy ring, followed by demethylation that gives rise to a catechol ring, which is in turn methylated by catecholmethyltransferase.² The aromatic pyrrolidine ring and side chain are subsequently

hydroxylated, followed by oxidation to the corresponding lactam, as well as ring opening to the corresponding carboxylic acid. It was documented that the demethylation step of the Phase I metabolism, in particular, is catalyzed through CYP450 isozymes 2C19, 2D6 and 1A2.³ Approximately 80% of MDPV remains unmetabolized, 10% is metabolized into catechol pyrovalerone, and 7% is metabolized into methylcatechol pyrovalerone. The high percentage of unmetabolized parent compound was postulated to result from the very high concentrations of MDPV added to liver microsome samples. Nevertheless, it was determined that the main metabolites further undergo Phase II glucuronidation and sulfation transformations to allow for renal excretion.²

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Elimination

The excretion profile of MDPV and its metabolites has not been studied in animals or humans. However, several reports have documented MDPV concentrations in urine samples obtained from patients presenting to hospital and poison centres, as well as opioid dependent patients undergoing opioid substitution treatment. MDPV concentrations in urine have been noted to range from 0.034 – 3.9 mg/L in those cases.⁴⁻⁶ While anecdotal reports indicate that users ingest anywhere between 5 – 30mg of MDPV per single session,⁶⁻⁸ variable dose intake among users and undocumented time since ingestion prohibit from determining the MDPV elimination half-life and concentration of excreted metabolites.

Pharmacological Mechanism of Action

The exact mechanism of action of MDPV has not been fully elucidated, with only a handful of studies investigating its neurobiological effects (references?). *In-vitro*, MDPV has demonstrated to act as a potent dopamine ($IC_{50} = 52.0 \pm 20$ nM) and norepinephrine ($IC_{50} = 28.3 \pm 8.1$ nM) reuptake inhibitor, exhibiting dopamine and norepinephrine reuptake inhibition 9 and 13 times greater than cocaine, respectively (references?). In contrast, inhibition of serotonin reuptake was found to be markedly less pronounced ($IC_{50} = 2780 \pm 590$ nM), a finding supported by the observed reduced binding affinity for the serotonergic transporter.⁹ Microdialysis studies in freely moving mice supported some of the *in-vitro* findings, showing that 60 minutes following oral administration of MDPV, extracellular striatum dopamine content was 2.1 times higher in the experimental group compared to those in the control group (references?). While significant, the MDPV-induced increases in dopamine levels were milder than those produced by the amphetamine-like stimulants methamphetamine and methylenedioxymethamphetamine (MDMA) (references?). Further, serotonin concentrations were not significantly influenced by MDPV administration.^{10, 11}

Comment [HABR4]: Can you add a bit more information on the exact in vitro model used here? Were they synaptosomes?

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Comment [HABR5]: I added "some" because the studies supported the dopamine observations but no information was provided for norepinephrine.
Comment [HABR6]: How much milder?
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Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. MDPV binding affinities at the dopamine transporter ($K_i = 21.4 \pm 4.6$ nM) and norepinephrine transporter ($K_i = 195 \pm 26$ nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively (references?). Binding affinity for the serotonin transporter was considerably lower ($K_i = 3770 \pm 560$ nM), indicating that MDPV is relatively inactive at this site.⁹

Comment [V7]: We are comparing binding affinities but I would like to see the link with the central nervous system
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Human Toxicology

At present, a toxicological profile for MDPV, including a dose-response relationship and the median lethal dose (LD₅₀), has not yet been established. Primary indication of MDPV toxicity derives from case reports documenting individuals presenting to hospital emergency departments after intake of “bath salts”. The most common symptoms of acute toxicity involve those associated with cardiovascular, neurological, and psychopathological function. Specifically, these symptoms include: tachycardia, chest pain, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, delusions, auditory and visual hallucinations, paranoid psychosis, agitation, aggression, anxiety, panic attacks, insomnia, memory loss, hyperthermia, rhabdomyolysis, abdominal pain, decreased appetite, vomiting, and kidney dysfunction.^{4, 12-17} Some effects such as sleeping difficulties, anxiety and agitation have been reported to persist for more than one day following ingestion,¹³ while others have been suggested to continue for as long as a week.¹⁵ Several cases of drug-induced delirium and even death have also been noted, where MDPV was the sole intoxicant.^{14,17} Most commonly, however, as MDPV is typically (often?) co-ingested with other substances, including benzodiazepines, amphetamines, cannabis, and ethanol,^{5, 18} it is unclear whether the list of acute toxic effects is purely a result of MDPV or a combination of drug-drug interactions.

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Evidence of Abuse Liability

Animal or human laboratory studies on abuse liability of MDPV have not been carried out. The most common approaches used to investigate abuse potential of drugs in animals, namely, self-administration tests, conditioned place-preference, drug discrimination, and psychomotor tests are not documented in the scientific literature. Similarly, abuse liability studies in recreational drug users using double-blind, randomized, double-dummy, placebo or positive comparator controlled, or crossover designs have not been conducted. Only one study has made an inference to MDPV being liable to abuse (reference?). Through the use of the gas chromatography-mass spectrometry (GC-MS) procedure to detect MDPV and other substances in urine of opioid-dependent patients undergoing opioid substitution treatment, the authors suggested that MDPV is mainly used as a “non-detectable” substitute for amphetamine primarily to increase concentration among users (reference). Moreover, the authors emphasized that the inability to detect MDPV through conventional immunoassay drug screenings is a notable factor that may contribute to the drug’s misuse.⁶

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Comment [HABR8]: Was this self-reported by the users?

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Comment [HABR9]: I think misuse in this context would suggest that MDPV has actual therapeutic utility. I think “abuse” would be a more appropriate term here??

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The numerous case reports of acute MDPV intoxication highlighted in the scientific literature may be in their own respect, an indirect indication that the drug may possess abuse potential. Among recreational drug users, it appears that MDPV may be gaining popularity, specifically for its anecdotally-described desirable subjective psychotropic effects. Synthesizing internet information on the effects of MDPV, one literature review has noted that specifically at low doses (undefined), MDPV is used to increase concentration, the capacity to work, and sexual

performance (reference?). Other desired psychotomimetic effects include increased sociability, energy, limited euphoria, and mild empathogenic effects.⁷

Evidence of Physical Dependence

Behavioural animal data on the reinforcing and physical dependence-producing effects of MDPV is not available. Clinical trials on MDPV abuse liability have also not been conducted, therefore scientific evidence of tolerance or withdrawal, which is critical to the definition of physical dependence, has not been observed. Although one literature source cited the “development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV”,⁷ these drug-related effects could not be confirmed.

Evidence of possible physical dependence and tolerance building effects is indirect and can only be gleaned from case studies and unverified internet information reported by users. Penders and Gestring¹⁴ reported a woman admitted to the psychiatric unit of a community hospital by way of an involuntary commitment initiated by her husband. The individual experienced fearful hallucinations of a home invasion that precipitated following daily use of MDPV for 2 weeks prior to admission. It is possible to infer that repeated and perhaps uncontrollable use of the drug is suggestive of physical dependence-like effects, however, this conclusion is highly speculative. Indication of possible tolerance is based on internet discussions documenting common redosing in a single session as well as using doses of over 200mg.⁷ Although MDPV is reported to have a short duration of action, use of doses well over 6 times the typical 5 to 30 mg used in a single ingestion, suggests that users may develop tolerance to the drug’s effects and thus possible physical dependence.

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Conclusions

The abuse potential assessment of a drug should be based on a composite analysis of chemistry, pharmacology, clinical data, health risks that the drug presents, as well as ease of access to the drug and administration. The limited pharmacological data suggests that MDPV is similar to other synthetic cathinones, inhibiting reuptake and stimulating the release of dopamine and norepinephrine. This mechanism of action has been associated with the production of amphetamine-like effects and is supported by user reports of stimulant and mild psychoactive effects similar to those of amphetamine and MDMA. Further, as the drug’s chemical structure allows it to be highly soluble and thus more easily cross the blood-brain barrier, a similar abuse liability profile to amphetamine may be expected. Taken together with the ease with which “bath salts” can be purchased, numerous routes of administration and unconfirmed user accounts of short duration of action, there may be preliminary indication that MDPV is likely to be abused. However, in the absence of clinical studies, by relying solely on sparse pharmacological data and indirect evidence suggestive of abuse liability, it is not possible to make a definitive statement of abuse liability.

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At present, there is no focused research on the dependence potential of MDPV and other synthetic cathinones. While dopaminergic properties, particularly in the mesocorticolimbic system, might be considered a signal suggesting the presence of reinforcing properties, sound scientific evidence that MDPV possesses dependence potential is not available. Therefore, it is not possible to conclude whether MDPV does or does not have dependence potential. (Maybe provide an explanation of the structural similarities with drugs in the CDSA, like pyrovalerone)

Comment [HABR10]: I would remove this sentence here as it adds new information that was not provided earlier in the text. Otherwise, it could be moved into the text at an earlier point and expanded upon.

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References

1. Yohannan JC, Bozenko JS. The characterization of 3,4-methylenedioxypropylvalerone. *Microgram Journal*. 2010;7:12-5.
2. Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom*. 2010;24(18):2706-14.
3. Meyer MR, Du P, Schuster F, Maurer HH. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-propylvalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom*. 2010;45(12):1426-42.
4. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin Syndrome Associated With MDPV Use: A Case Report. *Ann Emerg Med*. 2011.
5. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila)*. 2011;49(6):499-505.
6. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit*. 2011;33(2):257-63.
7. Coppola M, Mondola R. 3,4-methylenedioxypropylvalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett*. 2012;208(1):12-5.
8. Drug & Chemical Evaluation Section. 3,4-Methylenedioxypropylvalerone (MDPV). US Drug Enforcement Administration, Control OoD; 2011.
9. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem*. 2006;49(4):1420-32.
10. Fuwa T., Fukumori N., Tanaka T., Kubo Y., Ogata A., Uehara S., et al. Microdialysis study of drug effects on central nervous system. Changes in dopamine levels in mice striatum after oral administration of methylenedioxypropylvalerone [in Japanese]. *Tokyo-to Kenko Anzen Kenkyu Senta Kenkyu Nenpo*. 2007;58:287-92.
11. Fuwa T., Kodama T., Honda Y., Tanaka T., Kubo Y., Ohashi N., et al. Influence of Methylenedioxypropylvalerone on Central Nervous System - Using Microdialysis Methods [in Japanese]. *ChemBio*. 2009;5:62-72.
12. Centre for Disease Control and Prevention (CDC). Emergency department visits after the use of a drug sold as "bath salts". Michigan: 2011.
13. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, et al. Energy-1 ('NRG-1'): don't believe what the newspapers say about it being legal. *Emerg Med J*. 2011;28(12):1068-70.

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14. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: "Bath Salts". Gen Hosp Psychiatry. 2011;33(5):525-6.
15. Durham M. Ivory wave: the next mephedrone? Emerg Med J. 2011;28(12):1059-60.
16. Borek HA, Holstege CP. Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypropylvalerone. Ann Emerg Med. 2012.
17. Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypropylvalerone (MDPV). J Med Toxicol. 2012;8(1):69-75.
18. Kriikku P, Wilhelm L, Schwarz O, Rintatalo J. New designer drug of abuse: 3,4-Methylenedioxypropylvalerone (MDPV). Findings from apprehended drivers in Finland. Forensic Sci Int. 2011;210(1-3):195-200.

Comment [V11]: Should the references be in chronological order?

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Status Decisions for MDPV and MDPBP

Jocelyn Kula to: Suzanne Desjardins

Cc: Evelyn Soo, Tara Phillips

2012-05-01 02:13 PM

History: This message has been replied to.

Hi Suzanne,

An issue has come up with respect to the scheduling of 3,4-methylenedioxypropylvalerone (MDPV) under the CDSA and I am hoping we can meet sometime this week to discuss.

On March 7, 2012, Paul Loo of the CBSA wrote to Johanne (see attached letter) regarding an increase in the amount of MDPV being sampled for analysis and encouraging OCS to "continue its investigation and to have MDPV reviewed for scheduling". In his correspondence, he questions whether there is a need to go the scheduling route, as it is his view that MDPV can be considered controlled by virtue of the fact that it is very similar to a substance called MDPBP for which he previously received a "controlled" status decision.



Letter to Health Canada OCS 2012.pdf



MDPV Table.pdf

While we don't necessarily agree with Paul's characterization of MDPV, his correspondence does make us want to better understand the status decisions for both MDPV and MDPBP so that we can proceed with our Triage Statement and *Notice to interested parties* on MDPV. We also note that there are references in the literature to MDPV being an analogue of amphetamine by virtue of it belonging to the phenylethylamine group.

I will send you an invitation shortly.

Thanks in advance

Jocelyn

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire

Office of Controlled Substances/ Bureau des substances contrôlées

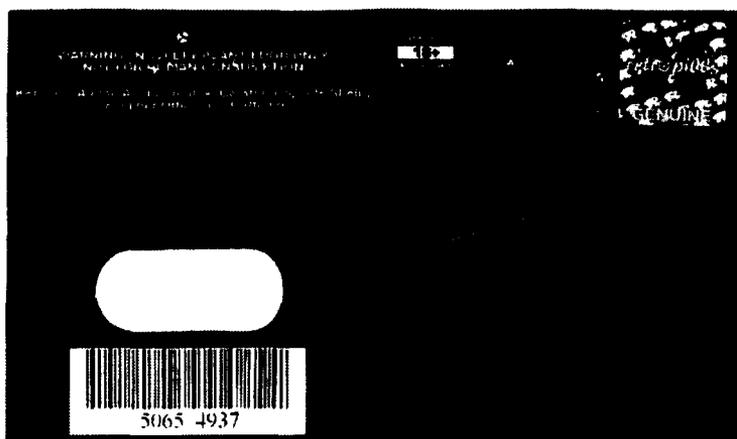
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada/ Santé Canada

Tel: (613) 946-0125 Fax: (613) 946-4224

CBSA Lab number	Amount	Declaration	Date reported
147508-001			June 27, 2006
150618-001			May 18, 2007
162339-002	75 g	6-bromo-2-methylquinoline (labelled as "Chem-29")	Jan 12, 2010
162560-003			Jan 18, 2010
163849-001		o-phthalimide	May 7, 2010
163896-001		2,3-dibromo-2-butene-1,4-diol	May 13, 2010
163896-002		2,3-dibromo-2-butene-1,4-diol	May 13, 2010
165204-001		MITSEEZ plant food (also contained butylone)**	Sept 16, 2010
165263-001	483 g	synephrine HCl (labelled as MDPV)	Sept 8, 2010
165263-002	34 g	synephrine HCl (labelled as MDPV)	Sept 8, 2010
165283-001		titanium dioxide	Aug 30, 2010
165283-002		titanium dioxide	Aug 30, 2010
165996-001		MOJO Novelty Bath Salts (also contained butylone)***	Nov 2, 2010
167348-001		MOJO Novelty Bath Salts (did not contain butylone)	April 7, 2011
167549-001		Bentonite: Montmorillonite	March 18, 2011
167567-001			March 22, 2011
167785-001/10	10 barrels (185 kg)	Labelled as MDPV - declared as methylamine	April 7, 2011
167786 (various sample numbers)	10 barrels (185 kg)	Labelled as MDPV - declaration unknown	April 6, 2011

**165204-001: the MDPV was in a capsule (brand name "MITSEEZ") in combination with butylone (also known as 2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one and bk-MBDB). Butylone is Schedule III CDSA. Here is a scan of the packaging from this product (outside and inside of the folded card holding the capsules):



have you tried them all?



MITSEEZ THOSE WEEDS!
Plant these capsules with your weeds and watch thum MITSEEZ!

retropills

For best results make sure your weeds have plenty of fluids and that no machinery is operated near them...

For more information and our full range of products visit the website
www.retropills.com

***165996-001: the MPDV was in powder form mixed with butylone in a product called "MOJO Novelty Bath Salts". Here is a scan of the packaging from this product (outside and inside of the folded card holding the capsules):

mojo
NOVELTY BATH SALTS ONLY
NOT FOR MEDICAL CONSUMPTION
INGREDIENTS:
Caffeine, Amino Acids Blend, Herbal Blend, Vitamin C, Aroon nut extract, Hydrate Concentrate

Manufactured in EU under license for Total Trading Ltd, Wales

www.themojoparty.com



6065 5994

mojo

GENUINE
DIESEL
PARTY

Restore your energy with a bath of mojo! simply add a normal sprinkle to the mix!

For best results make sure your bath has plenty of fluid and that no machinery is operated near it...

For more information and our full range of products visit the website
www.themojoparty.com



Re: Status Decisions for MDPV and MDPBP 
Jocelyn Kula to: Suzanne Desjardins
Cc: Evelyn Soo, Tara Phillips

2012-05-01 04:25 PM

Yes, I suppose we can wait. We are already off our workplan a little bit.....
Jocelyn

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224

Suzanne Desjardins Hi Jocelyn, Can the meeting be scheduled afte... 2012-05-01 04:06:47 PM

From: Suzanne Desjardins/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Cc: Evelyn Soo/HC-SC/GC/CA@HWC, Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-01 04:06 PM
Subject: Re: Status Decisions for MDPV and MDPBP

Hi Jocelyn,

Can the meeting be scheduled after May 7th? Evelyn's whole team is currently working on a massive ATI that is needed by then.

Thanks

Suzanne

Jocelyn Kula Hi Suzanne, An issue has come up with respect... 2012-05-01 02:13:45 PM

From: Jocelyn Kula/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC
Cc: Evelyn Soo/HC-SC/GC/CA@HWC, Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-01 02:13 PM
Subject: Status Decisions for MDPV and MDPBP

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On March 7, 2012, Paul Loo of the CBSA wrote to Johanne (see attached letter) regarding an increase in the amount of MDPV being sampled for analysis and encouraging OCS to "continue its investigation and to have MDPV reviewed for scheduling". In his correspondence, he questions whether there is a need to go the scheduling route, as it is his view that MDPV can be considered controlled by virtue of the fact that it is very similar to a substance called MDPBP for which he previously received a "controlled" status decision.

[attachment "Letter to Health Canada OCS 2012.pdf" deleted by Suzanne Desjardins/HC-SC/GC/CA]
[attachment "MDPV Table.pdf" deleted by Suzanne Desjardins/HC-SC/GC/CA]

While we don't necessarily agree with Paul's characterization of MDPV, his correspondence does make us want to better understand the status decisions for both MDPV and MDPBP so that we can proceed with our Triage Statement and *Notice to interested parties* on MDPV. We also note that there are references in the literature to MDPV being an analogue of amphetamine by virtue of it belonging to the phenylethylamine group.

I will send you an invitation shortly.

Thanks in advance
Jocelyn

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Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224



Re: Fw: Comments on MDPV report 
Hanan Abramovici to: Evelyn Soo

2012-05-02 08:27 AM

Hi Evelyn,

Yes, it was written by our contractor. He's done some very good work in the past. I forwarded my comments to Erin on Monday afternoon.

If you feel it necessary to look it over more closely, please go ahead and do so.

Thanks,
Hanan

Evelyn Soo

Hi Hanan I am assuming this was done by the c...

2012-05-01 10:11:56 AM

From: Evelyn Soo/HC-SC/GC/CA
To: Hanan Abramovici/HC-SC/GC/CA@HWC
Date: 2012-05-01 10:11 AM
Subject: Fw: Comments on MDPV report

Hi Hanan

I am assuming this was done by the contractor?

Vince is looking it over and I have taken a 2 sec glance and already seen a mistake. Pyrovalerone is not Schedule V, it is schedule IV.

I could take a closer look if you guys wish but I just needed to vent about using contractors.

See ya

Evelyn

Evelyn C Soo, PhD
A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
environnementale et de la sécurité des consommateurs (DGSESC)
Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
evelyn.soo@hc-sc.gc.ca
Telephone | Téléphone 613-952-2514
Government of Canada | Gouvernement du Canada

----- Forwarded by Evelyn Soo/HC-SC/GC/CA on 2012-05-01 10:10 AM -----

From: Erin Rutherford/HC-SC/GC/CA
To: Vincent Marleau/HC-SC/GC/CA@HWC
Cc: Evelyn Soo/HC-SC/GC/CA@HWC
Date: 2012-05-01 09:54 AM
Subject: Fw: Comments on MDPV report

Vincent,

I know your top priority is the ATI, but I know you have an interest in the drug issues, so this is just for your information.



Fw: Status Decisions for MDPV and MDPBP
Suzanne Desjardins to: Evelyn Soo

2012-05-02 08:10 AM

History: This message has been replied to.

Hi Evelyn,

This is your call. I am available.

Suzanne

----- Forwarded by Suzanne Desjardins/HC-SC/GC/CA on 2012-05-02 08:09 AM -----

From: Jocelyn Kula/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC
Cc: Evelyn Soo/HC-SC/GC/CA@HWC, Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-01 05:05 PM
Subject: Re: Status Decisions for MDPV and MDPBP

Actually Tara has just reminded me that she is not here at all the week of May 7-11 and I really want her to be there as this is her file. As pushing it to the week of May 14 is really too late for us (we are supposed to have our NOI out by end of May and it takes about 4 weeks to get all the approvals), is there any way we could meet quickly with you on the afternoon of May 4? I promise we will keep it to 30 mins tops tops.

Jocelyn

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
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From: Jocelyn Kula/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC



Re: Fw: OCS Comments on Draft MDPV assessment for consideration 
Hanan Abramovici to: Erin Rutherford

2012-05-02 02:19 PM

Hi Erin,
I can come by to discuss with you.
Thanks,
H.

Erin Rutherford Hanan, Do you have any suggestions or comme... 2012-05-02 02:13:16 PM

From: Erin Rutherford/HC-SC/GC/CA
To: Hanan Abramovici/HC-SC/GC/CA@HWC
Date: 2012-05-02 02:13 PM
Subject: Fw: OCS Comments on Draft MDPV assessment for consideration

Hanan,

Do you have any suggestions or comments about the comments from OCS? I'm not sure that I fully understand their comment about the characterization of MDPV.

If not, I will print them off and share them with Suzanne when I provide her with the draft which includes your comments

Thanks
Erin

----- Forwarded by Erin Rutherford/HC-SC/GC/CA on 2012-05-02 02:11 PM -----

From: Tara Phillips/HC-SC/GC/CA
To: Erin Rutherford/HC-SC/GC/CA@HWC
Cc: Jocelyn Kula/HC-SC/GC/CA@HWC, Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-05-02 02:06 PM
Subject: OCS Comments on Draft MDPV assessment for consideration

Hi Erin,

Thanks for the opportunity to comment on the draft MDPV assessment. Our comments are as follows:

- In paragraph 1, the final sentence should say that pyrovalerone is on Schedule IV to the CDSA (it says Schedule V right now and does not specifically reference the CDSA).

- Also in paragraph 1, could we say that MDPV is sold as a powder, crystal and pills since there have been reports of all three?

- For the Background and Chemical Structure sections, we need to consider the outstanding question of how we characterize MDPV. For example, in the Background paragraph, the statement that MDPV is one of a number of synthetic cathinones that are derivatives of the vegetable cathinone could be rejected if the decision is made to describe MDPV as a derivative of pyrovalerone.

- It would be very useful to strengthen the assessment in terms of abuse potential in two ways:
1) by highlighting or emphasizing the point about receptor binding affinities being many times that of cocaine for particular receptors and explicitly linking those affinities to abuse potential

2) by including references to anecdotal evidence of abuse, e.g., intensity of cravings, continued abuse despite significant adverse effects to users, etc.

- It would be helpful to include information about tolerance, if available.

Thank you,

Tara

----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2012-04-30 01:48 PM -----

From: Erin Rutherford/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-04-30 01:43 PM
Subject: Draft MDPV assessment for comments

Attached please find a draft MDPV assessment for your review and comments.
[attachment "MDPV Assessment DRAFT.doc" deleted by Erin Rutherford/HC-SC/GC/CA]

I would appreciate if you could provide me with any comments prior to COB Wednesday.

Regards

Erin Rutherford

Manager/Gestionnaire
Drugs and Alcohol Research/Recherche, drogues et alcool
Office of Research and Surveillance / Bureau de la recherche et de la surveillance
Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au
tabagisme
Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada / Santé Canada

123 Slater, MacDonald Building
Room A616 Address Locator: AL 3506 D
Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210
Fax: (613) 952-5188
E-mail: erin.rutherford@hc-sc.gc.ca



MDPV assessment
Hanan Abramovici to: Erin Rutherford

2012-05-03 09:56 AM



OCS comments draft MDPV Assessment.doc

MDPV Assessment

Comments provided by OCS and ORS response in red

Thanks for the opportunity to comment on the draft MDPV assessment. Our comments are as follows:

- In paragraph 1, the final sentence should say that pyrovalerone is on Schedule IV to the CDSA (it says Schedule V right now and does not specifically reference the CDSA). Agreed
- Also in paragraph 1, could we say that MDPV is sold as a powder, crystal and pills since there have been reports of all three? If confirmed by DAS?
- For the Background and Chemical Structure sections, we need to consider the outstanding question of how we characterize MDPV. For example, in the Background paragraph, the statement that MDPV is one of a number of synthetic cathinones that are derivatives of the vegetable cathinone could be rejected if the decision is made to describe MDPV as a derivative of pyrovalerone. Not appropriate for this document but certainly needs to be considered by OCS
- It would be very useful to strengthen the assessment in terms of abuse potential in two ways:
 - 1) by highlighting or emphasizing the point about receptor binding affinities being many times that of cocaine for particular receptors and explicitly linking those affinities to abuse potential. Receptor binding affinity does not say anything about a substance's abuse potential. Making such a prediction or assessment requires many different types of data (which include receptor binding studies, but also include *in vitro* efficacy/potency studies, *in vivo* behavioural studies and human data).
 - 2) by including references to anecdotal evidence of abuse, e.g., intensity of cravings, continued abuse despite significant adverse effects to users, etc. Not appropriate for this document but could be included by OCS in IAS
- It would be helpful to include information about tolerance, if available. Agreed (if data available)



Re: DAS information - MDPV 
Laura Petts to: Erin Rutherford
Cc: Judy Snider

2012-05-03 03:00 PM

I know I've done SOMETHING on it....I'll check through my e-mails etc to see if I can find anything.

Erin Rutherford

We are finishing up an assessment on one of th...

2012-05-03 01:46:27 PM

From: Erin Rutherford/HC-SC/GC/CA
To: Judy Snider/HC-SC/GC/CA@HWC
Cc: Laura Petts/HC-SC/GC/CA@HWC
Date: 2012-05-03 01:46 PM
Subject: DAS information - MDPV

We are finishing up an assessment on one of the "bath salts" MDPV 3,4-Methylenedioxypropylvalerone (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5yl)-2-pyrrolidin-1-yl-pentan-1-one) and as part of the background, are interested in the forms that it has been found/reported in Canada. Is there any data available? It is not currently scheduled.

If you guys don't have this info, any idea on a reputable source?

Thanks

Erin

Re: Draft MDPV Assessment 
Erin Rutherford to: Vlad Kushnir
Cc: Hanan Abramovici

2012-05-04 02:00 PM

Thank you so much for the excellent draft report.

Attached please find our comments/suggestions for the final report.

Please don't hesitate to contact me if you have any questions, comments or concerns.



MDPV Assessment DRAFT_HECSB_comments.doc
Erin Rutherford

Manager/Gestionnaire
Drugs and Alcohol Research/Recherche, drogues et alcool
Office of Research and Surveillance / Bureau de la recherche et de la surveillance
Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au tabagisme
Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada / Santé Canada

123 Slater, MacDonald Building
Room A616 Address Locator: AL 3506 D
Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210
Fax: (613) 952-5188
E-mail: erin.rutherford@hc-sc.gc.ca

Vlad Kushnir Good Day Erin, Please accept the attached draft... 2012-04-30 12:53:44 PM

From: Vlad Kushnir <[REDACTED]>
To: Erin Rutherford <erin.rutherford@hc-sc.gc.ca>
Cc: Hanan Abramovici <hanan.abramovici@hc-sc.gc.ca>
Date: 2012-04-30 12:53 PM
Subject: Draft MDPV Assessment

s.19(1)

Good Day Erin,

Please accept the attached draft report on MDPV abuse liability and dependence potential.

I look forward to your feedback. Best regards,

Vlad Kushnir[attachment "MDPV Assessment DRAFT.doc" deleted by Erin Rutherford/HC-SC/GC/CA]

3,4-Methylenedioxypropylone (MDPV) Abuse Liability and Dependence Potential Assessment

Prepared by Vlad Kushnir, MSc
April 30, 2012

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3,4-Methylenedioxypropylvalerone (MDPV) Abuse Liability and Dependence Potential Assessment

Background

The synthetic cathinone 3,4-Methylenedioxypropylvalerone, also known as MDPV, is a designer drug that is used for its stimulant-like psychoactive effects (reference?). First synthesized and patented by Boehringer Ingelheim in 1969,¹ it has only recently gained exposure among recreational drug users. It is one of a number synthetic cathinones that are derivatives of cathinone, a naturally occurring beta-ketone amphetamine analogue found in the leaves of *Catha edulis* (khat) (reference?). Synthetic cathinones are generally sold as “bath salts” or “plant food” and labelled “not for human consumption” to circumvent regulatory control and drug abuse legislation. As such, they are considered “legal highs”. MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities including(and provide references). The substance does not have any known medical uses and is an analogue of the compound propylvalerone (a Schedule V controlled substance).

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Comment [ER1]: Specify CDSA

Chemistry

Chemical Structure

The compound 3,4-Methylenedioxypropylvalerone (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5yl)-2-pyrrolidin-1-yl-pentan-1-one) is a pyrrolidine derivative of the synthetic cathinone propylvalerone, differing in the presence of a 3,4-methylenedioxy group linked to the aromatic ring.¹ Its molecular formula is C₁₆H₂₁NO₃ and it has a molecular weight of 275.34284 g/mol; Chemical Abstract Service Number 687603-66-3. MDPV is a solid at room temperature and has a melting point of 209.3 °C and a boiling point of 476 °C (reference?). It is available as an amorphous solid or crystalline powder that varies in colour, depending on composition and added impurities (reference). In the free base form it is brown or yellowish green, whereas as a hydrochloride salt it is white in appearance (reference).

Pharmacology

Biotransformation

Very little information is available regarding the biotransformation of MDPV and what little is known comes from only two *in vitro* studies (references). Examination of MDPV metabolism in human liver cells (intact cells? microsomes?) has prompted the proposal of a metabolic pathway that involves first, the opening of the methylenedioxy ring, followed by demethylation that gives rise to a catechol ring, which is in turn methylated by catecholmethyltransferase.² The aromatic pyrrolidine ring and side chain are subsequently hydroxylated, followed by oxidation to the corresponding lactam, as well as ring opening to the

Comment [HABR2]: Perhaps we should just stick to biotransformation or metabolism but not use both to ensure we are consistent in our terminology?

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corresponding carboxylic acid. It was documented that the demethylation step of the Phase I metabolism, in particular, is catalyzed through CYP450 isozymes 2C19, 2D6 and 1A2.³ Approximately 80% of MDPV remains unmetabolized, 10% is metabolized into catechol pyrovalerone, and 7% is metabolized into methylcatechol pyrovalerone. The high percentage of unmetabolized parent compound was postulated to result from the very high concentrations of MDPV added to liver microsome samples. Nevertheless, it was determined that the main metabolites further undergo Phase II glucuronidation and sulfation transformations to allow for renal excretion.²

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Elimination

The excretion profile of MDPV and its metabolites has not been studied in animals or humans. However, several reports have documented MDPV concentrations in urine samples obtained from patients presenting to hospital and poison centres, as well as opioid dependent patients undergoing opioid substitution treatment. MDPV concentrations in urine have been noted to range from 0.034 – 3.9 mg/L in those cases.⁴⁻⁶ While anecdotal reports indicate that users ingest anywhere between 5 – 30mg of MDPV per single session,⁶⁻⁸ variable dose intake among users and undocumented time since ingestion prohibit from determining the MDPV elimination half-life and concentration of excreted metabolites.

Pharmacological Mechanism of Action

The exact mechanism of action of MDPV has not been fully elucidated, with only a handful of studies investigating its neurobiological effects (references?). *In-vitro*, MDPV has demonstrated to act as a potent dopamine ($IC_{50} = 52.0 \pm 20$ nM) and norepinephrine ($IC_{50} = 28.3 \pm 8.1$ nM) reuptake inhibitor, exhibiting dopamine and norepinephrine reuptake inhibition 9 and 13 times greater than cocaine, respectively (references?). In contrast, inhibition of serotonin reuptake was found to be markedly less pronounced ($IC_{50} = 2780 \pm 590$ nM), a finding supported by the observed reduced binding affinity for the serotonergic transporter.⁹ Microdialysis studies in freely moving mice supported some of the *in-vitro* findings, showing that 60 minutes following oral administration of MDPV, extracellular striatum dopamine content was 2.1 times higher in the experimental group compared to those in the control group (references?). While significant, the MDPV-induced increases in dopamine levels were milder than those produced by the amphetamine-like stimulants methamphetamine and methylenedioxymethamphetamine (MDMA) (references?). Further, serotonin concentrations were not significantly influenced by MDPV administration.^{10, 11}

Comment [HABR3]: Can you add a bit more information on the exact in vitro model used here? Were they synaptosomes?

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Comment [HABR4]: I added "some" because the studies supported the dopamine observations but no information was provided for norepinephrine.

Comment [HABR5]: How much milder?
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Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. MDPV binding affinities at the dopamine transporter ($K_i = 21.4 \pm 4.6$ nM) and norepinephrine transporter ($K_i = 195 \pm 26$ nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively (references?). Binding affinity for the serotonin transporter was considerably lower ($K_i = 3770 \pm 560$ nM), indicating that MDPV is relatively inactive at this site.⁹

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Human Toxicology

At present, a toxicological profile for MDPV, including a dose-response relationship and the median lethal dose (LD₅₀), has not yet been established. Primary indication of MDPV toxicity derives from case reports documenting individuals presenting to hospital emergency departments after intake of “bath salts”. The most common symptoms of acute toxicity involve those associated with cardiovascular, neurological, and psychopathological function. Specifically, these symptoms include: tachycardia, chest pain, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, delusions, auditory and visual hallucinations, paranoid psychosis, agitation, aggression, anxiety, panic attacks, insomnia, memory loss, hyperthermia, rhabdomyolysis, abdominal pain, decreased appetite, vomiting, and kidney dysfunction.^{4, 12-17} Some effects such as sleeping difficulties, anxiety and agitation have been reported to persist for more than one day following ingestion,¹³ while others have been suggested to continue for as long as a week.¹⁵ Several cases of drug-induced delirium and even death have also been noted, where MDPV was the sole intoxicant.^{14, 17} Most commonly, however, as MDPV is typically (often?) co-ingested with other substances, including benzodiazepines, amphetamines, cannabis, and ethanol,^{5, 18} it is unclear whether the list of acute toxic effects is purely a result of MDPV or drug-drug interactions.

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Evidence of Abuse Liability

Animal or human laboratory studies on abuse liability of MDPV have not been carried out. The most common approaches used to investigate abuse potential of drugs in animals, namely, self-administration tests, conditioned place-preference, drug discrimination, and psychomotor tests are not documented in the scientific literature. Similarly, abuse liability studies in recreational drug users using double-blind, randomized, double-dummy, placebo or positive comparator controlled, or crossover designs have not been conducted. Only one study has made an inference to MDPV being liable to abuse (reference?). Through the use of the gas chromatography-mass spectrometry procedure to detect MDPV and other substances in urine of opioid-dependent patients undergoing opioid substitution treatment, the authors suggested that MDPV is mainly used as a “non-detectable” substitute for amphetamine primarily to increase concentration among users (reference). Moreover, the authors emphasized that the inability to detect MDPV through conventional immunoassay drug screenings is a notable factor that may contribute to the drug’s misuse.⁶

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Comment [HABR6]: Was this self-reported by the users?

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Comment [HABR7]: I think misuse in this context would suggest that MDPV has actual therapeutic utility. I think “abuse” would be a more appropriate term here??

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The numerous case reports of acute MDPV intoxication highlighted in the scientific literature may be in their own respect, an indirect indication that the drug may possess abuse potential. Among recreational drug users, it appears that MDPV may be gaining popularity specifically for its anecdotally-described desirable subjective psychotropic effects. Synthesizing internet information on the effects of MDPV, one literature review has noted that specifically at low doses (undefined), MDPV is used to increase concentration, the capacity to work, and sexual performance (reference?). Other desired psychotomimetic effects include increased sociability, energy, limited euphoria, and mild empathogenic effects.⁷

Evidence of Physical Dependence

Behavioural animal data on the reinforcing and physical dependence-producing effects of MDPV is not available. Clinical trials on MDPV abuse liability have also not been conducted, therefore tolerance or withdrawal, which is critical to the definition of physical dependence, has not been studied. Although one literature source cited the “development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV”,⁷ these drug-related effects could not be confirmed.

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Comment [ER8]: Can this be expanded on?

Evidence of possible physical dependence and tolerance building effects is indirect and can only be gleaned from case studies and unverified internet information reported by users. Penders and Gestring¹⁴ reported of a woman admitted to the psychiatric unit of a community hospital by way of an involuntary commitment initiated by her husband. The individual experienced fearful hallucinations of a home invasion that precipitated following daily use of MDPV for 2 weeks prior to admission. It is possible to infer that repeated and perhaps uncontrollable use of the drug is suggestive of physical dependence-like effects, however, this conclusion is highly speculative. Indication of possible tolerance is based on internet discussions documenting common redosing in a single session as well as using doses of over 200mg.⁷ Although MDPV is reported to have a short duration of action, use of doses well over 6 times the typical 5 to 30 mg used in a single ingestion, suggests that users may develop tolerance to the drug's effects and thus possible physical dependence.

Conclusions

The abuse potential assessment of a drug should be based on a composite analysis of chemistry, pharmacology, clinical data, health risks that the drug presents, as well as ease of access to the drug and administration. The limited pharmacological data suggests that MDPV is similar to other synthetic cathinones, inhibiting reuptake and stimulating the release of dopamine and norepinephrine. This mechanism of action has been associated with the production of amphetamine-like effects and is supported by user reports of stimulant and mild psychoactive effects similar to those of amphetamine and MDMA. Further, as the drug's chemical structure allows it to be highly soluble and thus more easily cross the blood-brain barrier, a similar abuse liability profile to amphetamine may be expected. Taken together with the ease with which “bath salts” can be purchased, numerous routes of administration and unconfirmed user accounts of short duration of action, there may be preliminary indication that MDPV is likely to be abused. However, in the absence of clinical studies, by relying solely on sparse pharmacological data and indirect evidence suggestive of abuse liability, it is not possible to make a definitive statement of abuse liability.

Comment [ER9]: Not covered previously – please add a paragraph in the pharmacology section on “routes”. HECSB will follow up with

Comment [HABR10]: I would remove this sentence here as it adds new information that was not provided earlier in the text. Otherwise, it could be moved into the text at an earlier point and expanded upon.

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At present, there is no focused research on the dependence potential of MDPV and other synthetic cathinones. While dopaminergic properties, particularly in the mesocorticolimbic system, might be considered a signal suggesting the presence of reinforcing properties, sound scientific

evidence that MDPV possesses dependence potential is not available. Therefore, it is not possible to conclude whether MDPV does or does not have dependence potential.

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References

1. Yohannan JC, Bozenko JS. The characterization of 3,4-methylenedioxypropylvalerone. *Microgram Journal*. 2010;7:12-5.
2. Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom*. 2010;24(18):2706-14.
3. Meyer MR, Du P, Schuster F, Maurer HH. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-propylvalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom*. 2010;45(12):1426-42.
4. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin Syndrome Associated With MDPV Use: A Case Report. *Ann Emerg Med*. 2011.
5. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila)*. 2011;49(6):499-505.
6. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit*. 2011;33(2):257-63.
7. Coppola M, Mondola R. 3,4-methylenedioxypropylvalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett*. 2012;208(1):12-5.
8. Drug & Chemical Evaluation Section. 3,4-Methylenedioxypropylvalerone (MDPV). US Drug Enforcement Administration, Control OoD; 2011.
9. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem*. 2006;49(4):1420-32.
10. Fuwa T., Fukumori N., Tanaka T., Kubo Y., Ogata A., Uehara S., et al. Microdialysis study of drug effects on central nervous system. Changes in dopamine levels in mice striatum after oral administration of methylenedioxypropylvalerone [in Japanese]. *Tokyo-to Kenko Anzen Kenkyu Senta Kenkyu Nenpo*. 2007;58:287-92.
11. Fuwa T., Kodama T., Honda Y., Tanaka T., Kubo Y., Ohashi N., et al. Influence of Methylenedioxypropylvalerone on Central Nervous System - Using Microdialysis Methods [in Japanese]. *ChemBio*. 2009;5:62-72.
12. Centre for Disease Control and Prevention (CDC). Emergency department visits after the use of a drug sold as "bath salts". Michigan: 2011.
13. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, et al. Energy-1 ('NRG-1'): don't believe what the newspapers say about it being legal. *Emerg Med J*. 2011;28(12):1068-70.

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14. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: "Bath Salts". Gen Hosp Psychiatry. 2011;33(5):525-6.
15. Durham M. Ivory wave: the next mephedrone? Emerg Med J. 2011;28(12):1059-60.
16. Borek HA, Holstege CP. Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypropylone. Ann Emerg Med. 2012.
17. Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypropylone (MDPV). J Med Toxicol. 2012;8(1):69-75.
18. Kriikku P, Wilhelm L, Schwarz O, Rintatalo J. New designer drug of abuse: 3,4-Methylenedioxypropylone (MDPV). Findings from apprehended drivers in Finland. Forensic Sci Int. 2011;210(1-3):195-200.

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MDPV Abuse Liability and Dependence Assessment

Erin Rutherford to: Jocelyn Kula, Tara Phillips

2012-05-16 01:55 PM

Cc: Suzanne Desjardins, Hanan Abramovici

Attached please find the final MDPV Abuse Liability and Dependence Assessment prepared for Health Canada by Vlad Kushnir.

Regards

Erin Rutherford

Manager/Gestionnaire

Drugs and Alcohol Research/Recherche, drogues et alcool

Office of Research and Surveillance / Bureau de la recherche et de la surveillance

Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au tabagisme

Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada / Santé Canada

123 Slater, MacDonald Building
Room A616 Address Locator: AL 3506 D
Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210

Fax: (613) 952-5188

E-mail: erin.rutherford@hc-sc.gc.ca



MDPV Assessment Final.doc

3,4-Methylenedioxypropylone (MDPV) Abuse Liability and Dependence Potential Assessment

Prepared by: Vlad Kushnir, MSc
May 11, 2012

3,4-Methylenedioxypropylone (MDPV) Abuse Liability and Dependence Potential Assessment

Background

The synthetic cathinone 3,4-Methylenedioxypropylone, also known as MDPV, is a designer drug that is used for its stimulant-like psychoactive effects.^{1, 2} First synthesized and patented by Boehringer Ingelheim in 1969,³ it has only recently gained exposure among recreational drug users. It is one of a number synthetic cathinones that are derivatives of cathinone, a naturally occurring beta-ketone amphetamine analogue found in the leaves of *Catha edulis* (khat).⁴ Synthetic cathinones are generally sold as “bath salts” or “plant food” and labelled “not for human consumption” to circumvent regulatory control and drug abuse legislation. As such, they are considered “legal highs”. MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities, with oral ingestion, injection, and nasal insufflation being most prevalent.^{2, 5} The substance does not have any known medical uses and is an analogue of the compound propylone (a Schedule V controlled substance under the Controlled Drugs and Substances Act).

Chemistry

Chemical Structure

The compound 3,4-Methylenedioxypropylone (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5yl)-2-pyrrolidin-1-yl-pentan-1-one) is a pyrrolidine derivative of the synthetic cathinone propylone, differing in the presence of a 3,4-methylenedioxy group linked to the aromatic ring.³ Its molecular formula is C₁₆H₂₁NO₃ and it has a molecular weight of 275.34284 g/mol; Chemical Abstract Service Number 687603-66-3. MDPV is a solid at room temperature and has a melting point of 238-239 °C.³ It is available as an amorphous solid or crystalline powder that varies in colour, depending on composition and added impurities.⁶ In the free base form it is brown or yellowish green, whereas as a hydrochloride salt it is white in appearance.¹

Pharmacology

Biotransformation

Very little information is available regarding the metabolism of MDPV and what little is known comes from only two *in vitro* studies.^{7, 8} Examination of MDPV metabolism in human liver microsomes has prompted the proposal of a metabolic pathway that involves first, the opening of the methylenedioxy ring, followed by demethylation that gives rise to a catechol ring, which is in turn methylated by catecholmethyltransferase.⁸ The aromatic pyrrolidine ring and side chain are subsequently hydroxylated, followed by oxidation to the corresponding lactam, as well as ring opening to the corresponding carboxylic acid. It was documented that the

demethylation step of the Phase I metabolism, in particular, is catalyzed through CYP450 isozymes 2C19, 2D6 and 1A2.⁷ Approximately 80% of MDPV remains unmetabolized, 10% is metabolized into catechol pyrovalerone, and 7% is metabolized into methylcatechol pyrovalerone. The high percentage of unmetabolized parent compound was postulated to result from the very high concentrations of MDPV added to liver microsome samples. Nevertheless, it was determined that the main metabolites further undergo Phase II glucuronidation and sulfation transformations to allow for renal excretion.⁸

Elimination

The excretion profile of MDPV and its metabolites has not been studied in animals or humans. However, several reports have documented MDPV concentrations in urine samples obtained from patients presenting to hospital and poison centres, as well as opioid dependent patients undergoing opioid substitution treatment. MDPV concentrations in urine have been noted to range from 0.034 – 3.9 mg/L in those cases.^{6, 9, 10} While anecdotal reports indicate that users ingest anywhere between 5 – 30mg of MDPV per single session,^{1, 10, 11} variable dose intake among users and undocumented time since ingestion prohibit from determining the MDPV elimination half-life and concentration of excreted metabolites.

Pharmacological Mechanism of Action

The exact mechanism of action of MDPV has not been fully elucidated, with only a handful of studies investigating its neurobiological effects.¹²⁻¹⁴ Binding assays evaluating inhibition of monoamine uptake in competition with [³H]dopamine, [³H]serotonin, and [³H]norepinephrine revealed that MDPV is a potent dopamine ($IC_{50} = 52.0 \pm 20$ nM) and norepinephrine ($IC_{50} = 28.3 \pm 8.1$ nM) reuptake inhibitor, exhibiting reuptake inhibition 9 and 13 times greater than cocaine, respectively.¹⁴ In contrast, inhibition of serotonin reuptake was found to be markedly less pronounced ($IC_{50} = 2780 \pm 590$ nM), a finding supported by the observed reduced binding affinity for the serotonergic transporter.¹⁴ Microdialysis studies in freely moving mice supported some of the *in-vitro* findings, showing that 60 minutes following oral administration of MDPV, extracellular striatum dopamine content was 2.1 times higher in the experimental group compared to those in the control group.¹² While significant, the MDPV-induced increases in dopamine levels were 3.5 times lower than those found to be produced by the amphetamine-like stimulants methamphetamine and methylenedioxymethamphetamine (MDMA) in the rat caudate.¹⁵ Further, serotonin concentrations were not significantly influenced by MDPV administration.^{12, 13}

Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. MDPV binding affinities at the dopamine transporter ($K_i = 21.4 \pm 4.6$ nM) and norepinephrine transporter ($K_i = 195 \pm 26$ nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively.¹⁴ Binding affinity for the serotonin transporter was considerably lower ($K_i = 3770 \pm 560$ nM), indicating that MDPV is relatively inactive at this site.¹⁴

Human Toxicology

At present, a toxicological profile for MDPV, including a dose-response relationship and the median lethal dose (LD₅₀), has not yet been established. Primary indication of MDPV toxicity is derived from case reports documenting individuals presenting to hospital emergency departments after intake of “bath salts”. The most common symptoms of acute toxicity involve those associated with cardiovascular, neurological, and psychopathological function. Specifically, these symptoms include: tachycardia, chest pain, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, delusions, auditory and visual hallucinations, paranoid psychosis, agitation, aggression, anxiety, panic attacks, insomnia, memory loss, hyperthermia, rhabdomyolysis, abdominal pain, decreased appetite, vomiting, and kidney dysfunction.^{5, 9, 16-20} Some effects such as sleeping difficulties, anxiety and agitation have been reported to persist for more than one day following ingestion,¹⁶ while others have been suggested to continue for as long as a week.¹⁸ Several cases of drug-induced delirium and even death have also been noted, where MDPV was the sole intoxicant.^{17, 20} However, as MDPV is most commonly co-ingested with other substances, including benzodiazepines, opiates, amphetamines, cannabis, and ethanol,^{1, 5, 6, 21} it is unclear whether the list of acute toxic effects is purely a result of MDPV or drug-drug interactions.

Routes of Administration

Information obtained from case reports and internet discussions about MDPV reveal that the drug is administered via a number of modalities. Routes of MDPV administration include intravenous, intramuscular, sublingual, oral ingestion, smoking, nasal insufflation, inhalation, as well as rectal administration.^{1,5,10, 20} Extrapolating from case reports of acute MDPV intoxication, it appears that the drug is most commonly administered by way of oral ingestion, nasal insufflation, or injection.^{16-18, 20}

Evidence of Abuse Liability

Animal or human laboratory studies on abuse liability of MDPV have not been carried out. The most common approaches used to investigate abuse potential of drugs in animals, namely, self-administration tests, conditioned place-preference, drug discrimination, and psychomotor tests are not documented in the scientific literature. Similarly, abuse liability studies in recreational drug users using double-blind, randomized, double-dummy, placebo or positive comparator controlled, or crossover designs have not been conducted. Only one study has made an inference to MDPV being liable to abuse.¹⁰ Through the use of the gas chromatography-mass spectrometry procedure to detect MDPV and other substances in urine of opioid-dependent patients undergoing opioid substitution treatment, the authors suggested that MDPV is mainly used as a “non-detectable” substitute for amphetamine. The inability to detect MDPV through conventional immunoassay drug screenings is indeed a notable factor that may contribute to the drug’s likelihood for abuse, especially among those wishing to conceal illicit drug use.¹⁰

The numerous case reports of acute MDPV intoxication highlighted in the scientific literature may be in their own respect, an indirect indication that the drug may possess abuse

potential. Among recreational drug users, it appears that MDPV may be gaining popularity specifically for its anecdotally-described desirable subjective psychotropic effects. Synthesizing internet information on the effects of MDPV, one literature review has noted that specifically at low doses (undefined), MDPV is used to increase concentration, the capacity to work, and sexual performance.¹ Other desired psychotomimetic effects include increased sociability, energy, limited euphoria, and mild empathogenic effects.¹ Based on information available on the internet, the European Union Commission funded Psychonaut Web Mapping Project, documented that MDPV has a relatively short duration of action, with peak effects occurring at 90 min post ingestion and lasting for approximately 1 hour.²² The various desirable effects and their duration vary greatly however, depending on dose and individual.

Evidence of Physical Dependence

Behavioural animal data on the reinforcing and physical dependence-producing effects of MDPV is not available. Clinical trials on MDPV abuse liability have also not been conducted, therefore tolerance or withdrawal, which is critical to the definition of physical dependence, has not been studied. Although one literature source cited the “development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV”,¹ it is unclear how this conclusion was reached and does not appear to be scientifically or clinically grounded.

Evidence of possible physical dependence and tolerance building effects is indirect and can only be gleaned from case studies and unverified internet information reported by users. Penders and Gestring¹⁷ reported of a woman admitted to the psychiatric unit of a community hospital by way of an involuntary commitment initiated by her husband. The individual experienced fearful hallucinations of a home invasion that precipitated following daily use of MDPV for 2 weeks prior to admission. It is possible to infer that repeated and perhaps uncontrollable use of the drug is suggestive of physical dependence-like effects, however, this conclusion is highly speculative. Indication of possible tolerance is based on internet discussions documenting frequent redosing in a single session as well as using doses of over 200mg.¹ Although MDPV is reported to have a short duration of action, use of doses well over 6 times the typical 5 to 30 mg used in a single ingestion, suggests that users may develop tolerance to the drug's effects and thus possible physical dependence.

Conclusions

The abuse potential assessment of a drug should be based on a composite analysis of chemistry, pharmacology, clinical data, health risks that the drug presents, as well as ease of access to the drug and administration. The limited pharmacological data suggests that MDPV is similar to other synthetic cathinones, inhibiting reuptake and stimulating the release of dopamine and norepinephrine. This mechanism of action has been associated with the production of amphetamine-like effects and is supported by user reports of stimulant and mild psychoactive effects similar to those of amphetamine and MDMA. Further, as the drug's chemical structure allows it to be highly soluble and thus more easily cross the blood-brain barrier, a similar abuse liability profile to amphetamine may be expected. Taken together with the ease with which “bath

salts” can be purchased, numerous routes of administration and unconfirmed user accounts of short duration of action, there may be preliminary indication that MDPV is likely to be abused. However, in the absence of clinical studies, by relying solely on sparse pharmacological data and indirect evidence suggestive of abuse liability, it is not possible to make a definitive statement of abuse liability.

At present, there is no focused research on the dependence potential of MDPV and other synthetic cathinones. Sound scientific evidence that MDPV possesses dependence potential is not available. It is therefore not possible to conclude whether MDPV does or does not possess dependence potential.

References

1. Coppola M, Mondola R. 3,4-methylenedioxypropylone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett.* 2012;208(1):12-5.
2. Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol.* 2012;8(1):33-42.
3. Yohannan JC, Bozenko JS. The characterization of 3,4-methylenedioxypropylone. *Microgram Journal.* 2010;7:12-5.
4. Hassan NA, Gunaid AA, Murray-Lyon IM. Khat (*Catha edulis*): health aspects of khat chewing. *East Mediterr Health J.* 2007;13(3):706-18.
5. Centre for Disease Control and Prevention (CDC). Emergency department visits after the use of a drug sold as "bath salts". Michigan: 2011.
6. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila).* 2011;49(6):499-505.
7. Meyer MR, Du P, Schuster F, Maurer HH. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-propylone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom.* 2010;45(12):1426-42.
8. Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom.* 2010;24(18):2706-14.
9. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin Syndrome Associated With MDPV Use: A Case Report. *Ann Emerg Med.* 2011.
10. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit.* 2011;33(2):257-63.
11. Drug & Chemical Evaluation Section. 3,4-Methylenedioxypropylone (MDPV). US Drug Enforcement Administration, Control OoD; 2011.
12. Fuwa T., Fukumori N., Tanaka T., Kubo Y., Ogata A., Uehara S., et al. Microdialysis study of drug effects on central nervous system. Changes in dopamine levels in mice striatum after oral administration of methylenedioxypropylone [in Japanese]. *Tokyo-to Kenko Anzen Kenkyu Senta Kenkyu Nenpo.* 2007;58:287-92.
13. Fuwa T., Kodama T., Honda Y., Tanaka T., Kubo Y., Ohashi N., et al. Influence of Methylenedioxypropylone on Central Nervous System - Using Microdialysis Methods [in Japanese]. *ChemBio.* 2009;5:62-72.

14. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem.* 2006;49(4):1420-32.
15. Gough B, Imam SZ, Blough B, Slikker W, Jr., Ali SF. Comparative effects of substituted amphetamines (PMA, MDMA, and METH) on monoamines in rat caudate: a microdialysis study. *Ann N Y Acad Sci.* 2002;965:410-20.
16. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, et al. Energy-1 ('NRG-1'): don't believe what the newspapers say about it being legal. *Emerg Med J.* 2011;28(12):1068-70.
17. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: "Bath Salts". *Gen Hosp Psychiatry.* 2011;33(5):525-6.
18. Durham M. Ivory wave: the next mephedrone? *Emerg Med J.* 2011;28(12):1059-60.
19. Borek HA, Holstege CP. Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypropylpyrovalerone. *Ann Emerg Med.* 2012.
20. Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypropylpyrovalerone (MDPV). *J Med Toxicol.* 2012;8(1):69-75.
21. Kriikku P, Wilhelm L, Schwarz O, Rintatalo J. New designer drug of abuse: 3,4-Methylenedioxypropylpyrovalerone (MDPV). Findings from apprehended drivers in Finland. *Forensic Sci Int.* 2011;210(1-3):195-200.
22. Psychonaut Web Mapping Group. MDPV Report. London, United Kingdom: Institute of Psychiatry, Kings's College, 2010.

Protected B Draft

Record of Discussion (ROD)
Controlled Substances Scheduling (CSS) Working Group Meeting
Wednesday, May 16 2012, 1:30-3:00pm
123 Slater Street, Rm 305A

<p>Present:</p> <ul style="list-style-type: none">• Suzanne Desjardins, Office of Research and Surveillance (ORS), Controlled Substances and Tobacco Directorate (CSTD), (HECSB) (Chair)• Denis Arsenault, Office of Controlled Substances (OCS), CSTD, HECSB• Claudia Campos, Border Integrity Unit, HPFB• Stephanie Chandler, OCS, CSTD, HECSB• Hanar Abramovici, ORS, CSTD, HECSB• Bruna Brands, ORS, CSTD, HECSB via phone• Robin Marles, Bureau of Clinical Trials and Health Sciences, NHPD, HPFB• Tanja Kalajdzic, Marketed Pharmaceuticals & Medical Devices Division, (HPFB)• Evelyn Soo, ORS, CSTD, HECSB	<p>Regrets:</p> <ul style="list-style-type: none">• André Fouquet, Drug Analysis Service– Quebec Region, Regions and Programs Branch (RAPB)• Ann Kourtesis, Border Integrity Unit, HPFB• Jocelyn Kula, OCS, CSTD, HECSB• Johanne Beaulieu, OCS, CSTD, HECSB <p>Secretariat:</p> <ul style="list-style-type: none">• Tiffany Thornton (Secretariat) ORS, CSTD, HECSB
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1. Welcome & Introductions

Suzanne welcomed the CSS-WG members. She advised the WG that a replacement would need to be found for Colette Strand, Office of Science, TPD who has taken a new position. Suzanne indicated that she would approach management from the TPD to identify a new representative.

Robin noted that his title and position has changed to Senior Science Advisor, Bureau of Policy and Risk Management, Natural Health Products Directorate, Health Products and Food Branch.

2. Approval of Agenda Items

Item 6 – Update on Salvia would be provided by Denis in Johanne's absence

3. Approval of ROD March 14, 2012

ROD approved with minor edits

- spelling of dextromethorphan

- delete 1st action item under Item 5 – Update/s on MDPV.

s.20(1)(b)

4. Update on [REDACTED]

Tanja indicated that post market data collection on the abuse of [REDACTED] has been quite difficult. As a result there has been some preliminary discussions within the Marketed Pharmaceuticals & Medical Devices Division about the possibility of having an external researcher collect evidence other than the spontaneous data that is collected within the Division. Tanja noted that if proposals are solicited from external researchers there will be an opportunity for the CSS-WG to comment.

Actions:

- Tanja will update the CSS-WG about the status of the proposals at the next meeting
- Claudia indicated that she has data related to [REDACTED] but still need regional approval. After this is sought she will forward the information to the CSS-WG

5. Update on [REDACTED]

Tanja indicated that the UK will withdraw [REDACTED] from the market in the next 15 months because the risk mitigation measures implemented have not been effective in reducing the harms related to this substance.

Tanja noted that drug is not sold much in Canada. It is indicated for the relief from emotional stress, headaches and migraines. Bruna indicated that this drug is not used in Canada very much as there are better medications currently on the market to address these symptoms.

Actions:

- To gather more information on the use of [REDACTED] in Canada Suzanne will request data related to seizures, Denis will check the evidence related to loss and theft and Claudia will follow-up with the border committee.

6. Salvia

Denis indicated that a briefing was held with the Director General of CSTD in March 2012 on Salvia. It was decided not proceed with the scheduling of *Salvia divinorum* and *salvinorin A* in Schedule III on the *Controlled Drugs and Substances Act* (CDSA) and the Schedule to Part J of the *Food and Drug*

Regulations (FDR). This decision was primarily based on limited evidence, of “harms” of *Salvia divinorum* and *salvinorin A* (including overdose, deaths, injuries, ER visits). Denis noted that *Its Your Health* is currently being updated to remove any references made to scheduling.

Suzanne indicated that it will be important to review the current framework under which the CSS-WG operates. Discussions related to this issue will be held at the next meeting where Johanne Beaulieu, Director of OCS will be invited to attend.

Actions:

- An invitation for the meeting in June will be extended to Johanne Beaulieu to seek clarification regarding the current framework for scheduling and role of the CSS-WG.

7. Update on the WHO 35th ECDD

Bruna indicated that all the pre-review and peer review documents and the agenda for the upcoming ECDD meeting on June 4-8th in Tunisia are now available online

(http://www.who.int/medicines/areas/quality_safety/35thecddmeet/en/index.html) including dextromethorphan (an active ingredient in cough syrup).

Bruna noted that there have been recent published scientific review articles discussing the abuse of dextromethorphan among youth and increasing numbers of ER presentations due to adverse events. She indicated that recent evidence suggests that when “super doses” (about 10x the recommended dose) are consumed dissociative effects occur. The 2010 OSDUHS reports that approximately 1 in 10 students (grades 7-12) have abused dextromethorphan for its psychotropic effect in their lifetime and 4% to 7% of students have abused in the past year. The upcoming release of the Youth Smoking Survey (YSS) on May 30th, 2012 will also provide results on the abuse of dextromethorphan among youth in Canada.

Actions:

- Brunna will report back to the CSS-WG on the discussions related to dextromethorphan from the ECDD meeting
- Suzanne to circulate results from the YSS when it is release on May 31th, 2012

8. Update/s on emerging issues

Evelyn inquired if CSS-WG had heard of a substance called “whack” a street drug that contains a mixture of 4-fluorotropacocaine and desoxyipradrol. Currently, neither of these substances is controlled under the CDSA as there are no provisions to include cocaine analogs under the existing schedules. She also noted that more frequent requests for the status of cocaine analogues have recently been made including two recent separate (but related) requests for 4-fluorotropacocaine and desoxyipradrol which led her to the discovery of “whack.”

Actions:

- Bruna indicated that she will discuss with colleagues at the ECDD meeting and try to gather more information. She will report back to the CSS-WG upon her return.

9. Next Steps

- Tiffany to circulate the agenda and ROD from prior to the next meeting on June 20th, 2012.



For Comments: Draft MDPV Notice
Tara Phillips to: Suzanne Desjardins
Cc: Jocelyn Kula

2012-05-28 04:28 PM

History: This message has been forwarded.

Hi Suzanne,

Please find attached, for your review, a draft *Notice to interested parties* regarding the proposed scheduling of MDPV under the CDSA.



NOI MDPV 2012-05-28.doc

Please send any comments by close of business on Wednesday, May 30th. The aim is to publish the Notice as soon as possible but no later than the end of June.

Thank you,

Tara

Tara Phillips

Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

Notice to interested parties – Proposed amendment to Schedule III to the *Controlled Drugs and Substances Act*

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's intent to add 3,4-methylenedioxypropylone (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule III to the *Controlled Drugs and Substances Act* (CDSA).

MDPV is a synthetic designer drug that is used for its stimulant-like psychoactive effects. While little is known about the specific health effects associated with the use of MDPV, the use of stimulants in general may significantly increase blood pressure, heart rate and pulse. MDPV use has also been associated with severe panic attacks and anxiety, as well as hallucinations and psychosis.

Although MDPV is not listed in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have already elected to regulate it as a controlled substance including the United States, Australia, Denmark, Sweden and the United Kingdom.

Health Canada is not aware of any legitimate medical, scientific or industrial applications for MDPV and is therefore not intending to regulate MDPV in accordance with existing regulatory schemes under the CDSA.

Health Canada is proposing to include MDPV in Schedule III to the CDSA in order to prohibit the following activities with this substance: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The scheduling of MDPV will also ensure law enforcement can take action against all suspected illegal activities involving MDPV.

This proposed action is in response to concerns expressed by health officials and recent increases in law enforcement and border seizures of products labelled as "bath salts". Such products are not genuine bath salt products intended for softening and/or cleansing the skin, but contain one or more substances with stimulant properties including mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and MDPV. While the extent of their use in Canada is unknown, "bath salt" products are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky".

The publication of this notice begins a 60-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo,

Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D,
123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email
at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. In particular, parties
involved in legitimate activities involving MDPV are encouraged to respond to inform
Health Canada's decision with respect to regulation of MDPV under the CDSA.

CATHY SABISTON
Director General
Controlled Substance and Tobacco Directorate



Re: Fw: For Comments: Draft MDPV Notice 

Hanan Abramovici to: Suzanne Desjardins
Cc: Erin Rutherford, Evelyn Soo, Judy Snider

2012-05-29 04:32 PM

History: This message has been replied to.

Hi Suzanne,
Please find my (very few) comments.
Thanks,
Hanan



NOI MDPV 2012-05-28_HA.doc

Suzanne Desjardins please send me any comments by 4:00pm tom...

2012-05-29 04:24:23 PM

From: Suzanne Desjardins/HC-SC/GC/CA
To: Evelyn Soo/HC-SC/GC/CA@HWC, Hanan Abramovici/HC-SC/GC/CA@HWC
Cc: Erin Rutherford/HC-SC/GC/CA@HWC, Judy Snider/HC-SC/GC/CA@HWC
Date: 2012-05-29 04:24 PM
Subject: Fw: For Comments: Draft MDPV Notice

please send me any comments by 4:00pm tomorrow

Thanks

Suzanne

----- Forwarded by Suzanne Desjardins/HC-SC/GC/CA on 2012-05-29 04:21 PM -----

From: Tara Phillips/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC
Cc: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-05-28 04:28 PM
Subject: For Comments: Draft MDPV Notice

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[attachment "NOI MDPV 2012-05-28.doc" deleted by Hanan Abramovici/HC-SC/GC/CA]

Please send any comments by close of business on Wednesday, May 30th. The aim is to publish the Notice as soon as possible but no later than the end of June.

Thank you,

Tara

Tara Phillips

Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada

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Although MDPV is not listed in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have already elected to regulate it as a controlled substance including the United States, Australia, Denmark, Sweden and the United Kingdom.

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CATHY SABISTON
Director General
Controlled Substance and Tobacco Directorate



Re: Fw: For Comments: Draft MDPV Notice 
Suzanne Desjardins to: Tara Phillips
Cc: Jocelyn Kula, Evelyn Soo, Hanan Abramovici

2012-05-30 04:20 PM

Hi Tara,

We only have 1 suggested addition:



NOI MDPV 2012-05-28_HA.doc

One point that Evelyn raised is with the impact of C10 (moving amphetamines from schedule III to schedule I). I assume that it has been considered in the scheduling of MDPV. Does it mean that it will be moved automatically to schedule I when C10 becomes effective?

Thanks

Suzanne

Tara Phillips

Hi Suzanne, Would it be possible to have any co...

2012-05-30 01:29:23 PM

From: Tara Phillips/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC
Cc: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-05-30 01:29 PM
Subject: Fw: For Comments: Draft MDPV Notice

Hi Suzanne,

Would it be possible to have any comments from ORS at your earliest convenience? Cathy's aim is now to have the Notice to Canada Gazette by this Friday for publication the following Saturday. Cathy has asked to see the final Notice by COB today for her approval.

Thank you,

Tara
946-6521

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-30 01:28 PM -----

From: Tara Phillips/HC-SC/GC/CA
To: Suzanne Desjardins/HC-SC/GC/CA@HWC
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Health Canada is not aware of any legitimate medical, scientific or industrial applications for MDPV and is therefore not intending to regulate MDPV in accordance with existing regulatory schemes under the CDSA.

Health Canada is proposing to include MDPV in Schedule III to the CDSA in order to prohibit the following activities with this substance: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The scheduling of MDPV will also ensure law enforcement can take action against all suspected illegal activities involving MDPV.

This proposed action is in response to concerns expressed by health officials and recent increases in law enforcement and border seizures of products labelled as "bath salts". Such products are not genuine bath salt products intended for softening and/or cleansing the skin, but contain one or more substances with stimulant properties including mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and MDPV. While the extent of their use in Canada is unknown, "bath salt" products are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky".

The publication of this notice begins a 60-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D, 123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. In particular, parties involved in legitimate activities involving MDPV are encouraged to respond to inform Health Canada's decision with respect to regulation of MDPV under the CDSA.

CATHY SABISTON
Director General
Controlled Substance and Tobacco Directorate



Fw: CTV.ca/health - Bath salts becoming a growing drug problem

Denis Arsenault to: Salha Jumbe

2011-01-24 10:54 AM

Denis Arsenault Fw: CTV.ca/health - Bath salts becoming a growing drug problem

Hi Salha,

Can we discuss upon your return? Thanks

Denis

Denis Arsenault, A/Manager / Gestionnaire p.i.
Regulatory Policy Division /
Division des politiques réglementaires,
Office of Controlled Substances /
Bureau des substances contrôlées,
Health Canada / Santé Canada
Tel/Tél: (613) 957-6828
Fax / Télécopieur : (613) 946-4224
E-Mail/Courriel: denis_arsenault@hc-sc.gc.ca

----- Forwarded by Denis Arsenault/HC-SC/GC/CA on 2011-01-24 10:53 AM -----

From: Jocelyn Kula/HC-SC/GC/CA
To: Denis Arsenault/HC-SC/GC/CA@HWC
Date: 2011-01-24 10:46 AM
Subject: Fw: CTV.ca/health - Bath salts becoming a growing drug problem

fyi
also pls add to mephedrone

JK

Jocelyn Kula
Acting Director/ Directrice par intérim
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 952-2177 Fax: (613) 946-4224
----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2011-01-24 10:45 AM -----

From: Suzanne Desjardins/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC, Stephanie Szick/HC-SC/GC/CA@HWC
Cc: Hanan Abramovici/HC-SC/GC/CA@HWC, Evelyn Soo/HC-SC/GC/CA@HWC

Date: 2011-01-24 09:41 AM
Subject: Fw: CTV.ca/health - Bath salts becoming a growing drug problem

Hanan just reminded me that the terms "bath salts" and "plant food" have been linked to mephedrone (see the fact sheet he had prepared last fall on new drugs, which included mephedrone). I think we can assume that these substances are not used as bath salts or plant food and that they are just names under which they are sold.

↳ not Epson salts - MSJ
no legitimate use - MSJ



New Drug Fact Sheets Oct 22 2010.doc

Suzanne

----- Forwarded by Suzanne Desjardins/HC-SC/GC/CA on 2011-01-24 09:37 AM -----

From: Suzanne Desjardins/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC, Stephanie Szick/HC-SC/GC/CA@HWC
Date: 2011-01-24 09:02 AM
Subject: Fw: CTV.ca/health - Bath salts becoming a growing drug problem

additional information from Evelyn Soo:

MDPV is most often sold as "bath salts" in Europe, particularly in the UK, and is **not** controlled in Canada. I haven't come across the marketing of mephedrone as bath salts but wouldn't be surprised at the same time.

----- Forwarded by Suzanne Desjardins/HC-SC/GC/CA on 2011-01-24 09:00 AM -----

From: Suzanne Desjardins/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Cc: Cathy A Sabiston/HC-SC/GC/CA@HWC, Stephanie Szick/HC-SC/GC/CA@HWC
Date: 2011-01-24 08:54 AM
Subject: Re: CTV.ca/health - Bath salts becoming a growing drug problem

we are looking at seizure data but there was a media query on this last August (appended below for your information). The connection to "bath salts" is new to me too.
Suzanne

Christine
Roush/HC-SC/GC/CA
2010-08-18 04:29 PM

To Cathy A Sabiston/HC-SC/GC/CA@HWC
cc CSTD-DGO, Diane Allan/HC-SC/GC/CA@HWC, Jeannine Ritchot/HC-SC/GC/CA@HWC, Denis Arsenault/HC-SC/GC/CA@HWC, Evelyn Soo/HC-SC/GC/CA@HWC, Nicole Prentice/HC-SC/GC/CA@HWC, Dave Stephens/HC-SC/GC/CA@HWC

Subject Fw: For approval: Media query - Montreal Gazette - [REDACTED]
[REDACTED] Ecstasy-like drug "Mephedrone"

s.19(1)

Cathy - for your approval please before 5pm. Thanks,

000108

Approved by: Jeannine Ritchot, A/Director, OCS
Suzanne Desjardins, Director, ODARS

Here is the Montreal Gazette enquiry for your approval asap. We have included below a link to the advisory issued by the Quebec Ministry of Health on this drug.

Thanks again.

Gazette is bouncing from a Quebec Ministry of Health issuance on Mephedrone due to a hospitalization of a user; drawing attention to this substance. reporter wants to know more about the drug, what it's legal status is, and what it is intended for.

<http://communiqués.gouv.qc.ca/gouvqc/communiqués/GPQF/Aout2010/17/c3251.html>

Re: legal extacy

Q1 - Mephedrone / cathinone: Is it legal?

A1- Mephedrone is a synthetic amphetamine-type stimulant also known as 4-methylmethcathinone. It is regulated as a controlled substance because it is an analog of amphetamine (specifically, 4-methylmethamphetamine), which is included in Schedule III to the *Controlled Drugs and Substances Act*. Mephedrone is illegal in Canada. Unless authorized by regulation, all activities with mephedrone, such as production, importation, exportation, possession, are prohibited in Canada.

Q2 - Health Quebec released statement yesterday - required hospitalization and intensive care due to drug; Is it a Schedule 3 controlled substance?

A2- See A1.

Q3 - What is it intended for (if there is a legal use?)

A3- There is no known legitimate, therapeutic use for mephedrone in Canada.

Q4 - Is this drug a priority for HC? Would HC be issuing a similar statement?

A4 - As noted above, Mephedrone is illegal in Canada and there is no known, legitimate, therapeutic use for it in Canada.

Q5 - Is HC aware of other adverse reactions as a result of this drug?

A5 - There exists little scientific information regarding mephedrone. However, statements have been made suggesting that its effects include increased alertness, euphoria, and excitement. Adverse effects associated with its use include nose bleeds, hallucinations, paranoia, nausea and vomiting. Since mephedrone is an amphetamine-type stimulant, more general adverse effects associated with such stimulants can include seizures, cerebral hemorrhage, high fever, coma or death. Amphetamines can also increase heart rate and blood pressure and effects such as palpitations, irregular or abnormal heartbeat, heart attack, and cardiovascular collapse.

Christine Roush
Senior Communications Advisor/

2

Jocelyn Kula Mephedrone is already controlled in Canada as... 2011-01-24 08:33:02 AM

From: Jocelyn Kula/HC-SC/GC/CA
To: Cathy A Sabiston/HC-SC/GC/CA@HWC, Stephanie Szick/HC-SC/GC/CA@HWC, Suzanne
 Desjardins/HC-SC/GC/CA@HWC
Date: 2011-01-24 08:33 AM
Subject: Re: CTV.ca/health - Bath salts becoming a growing drug problem

Mephedrone is already controlled in Canada as an analog of cathinone (which is in Schedule IV (or III will have to confirm, always get cathinone and cathine mixed up). Cathinone is also not included in schedules to any of our regs which means there is no legal way to import, export, produce except under special authorization from HC (research exemption). Suzanne can probably comment on seizure incidence but I know we have done previous enquiries....just hadn't heard of the bath salt connection.

JK

Cathy A Sabiston

----- Original Message -----

From: Cathy A Sabiston
Sent: 2011-01-24 08:20 AM EST
To: Jocelyn Kula; Stephanie Szick; Suzanne Desjardins
Subject: Fw: CTV.ca/health - Bath salts becoming a growing drug problem

I'm sure we can expect enquiries today. Do we have any data/knowledge?

HC_Media_SC

----- Original Message -----

From: HC_Media_SC
Sent: 2011-01-24 07:46 AM EST
Subject: CTV.ca/health - Bath salts becoming a growing drug problem

Distribution group/Groupe de distribution: Controlled Substances - Substances contrôlées -
HECSB/DGSESC, Consumer Product Safety - Sécurité des produits de consommation -
HECSB/DGSESC,

CTV.ca/health

Bath salts becoming a growing drug problem

<http://www.ctv.ca/CTVNews/Health/20110122/bath-salts-drug-110122/>

FULTON, Miss. – When Neil Brown got high on bath salts, he took his skinning knife and slit his face and stomach repeatedly. Brown survived, but authorities say others haven't been so lucky after snorting, injecting or smoking powders with such innocuous-sounding names as Ivory Snow, Red Dove and Vanilla Sky.

Some say the effects of the powders are as powerful as abusing methamphetamine. Increasingly, law enforcement agents and poison control centers say the bath salts with complex chemical names are an emerging menace in several U.S. states where authorities talk of banning their sale.

From the Deep South to California, emergency calls are being reported over exposure to the stimulants the powders often contain: mephedrone and methylenedioxypyrovalerone, also known as MDPV.

Sold under such names as Ivory Wave, Bliss, White Lightning and Hurricane Charlie, the chemicals can cause hallucinations, paranoia, rapid heart rates and suicidal thoughts, authorities say. The chemicals are in bath salts and even plant foods that are sold legally at convenience stores and on the Internet. However, they aren't necessarily being used for the purposes on the label.

Mississippi lawmakers this week began considering a proposal to ban the sale of the powders, and a

similar step is being sought in Kentucky. In Louisiana, the bath salts were outlawed by an emergency order after the state's poison center received more than 125 calls in the last three months of 2010 involving exposure to the chemicals.

In Brown's case, he said he had tried every drug from heroin to crack and was so shaken by terrifying hallucinations that he wrote one Mississippi paper urging people to stay away from the bath salts.

"I couldn't tell you why I did it," Brown said, pointing to his scars. "The psychological effects are still there."

While Brown survived, sheriff's authorities in one Mississippi county say they believe one woman overdosed on bath salts there. In southern Louisiana, the family of a 21-year-old man says he cut his throat and ended his life with a gunshot. Authorities are investigating whether a man charged with capital murder in the December death of a Tippah County, Miss., sheriff's deputy was under the influence of the bath salts.

The stimulants aren't regulated by the U.S. Drug Enforcement Administration, but are facing federal scrutiny. Law officers say some of the substances are being shipped from Europe, but origins are still unclear.

Gary Boggs, an executive assistant at the DEA, said there's a lengthy process to restrict these types of designer chemicals, including reviewing the abuse data. But it's a process that can take years.

Dr. Mark Ryan, director of Louisiana's poison control center, said he thinks state bans on the chemicals can be effective. He said calls about the salts have dropped sharply since Louisiana banned their sale in January.

Ryan said cathinone, the parent substance of the drugs, comes from a plant grown in Africa and is regulated. He said MDPV and mephedrone are made in a lab, and they aren't regulated because they're not marketed for human consumption. The stimulants affect neurotransmitters in the brain, he said.

"It causes intense cravings for it. They'll binge on it three or four days before they show up in an ER. Even though it's a horrible trip, they want to do it again and again," Ryan said.

Ryan said at least 25 states have received calls about exposure, including Nevada and California. He said Louisiana leads with the greatest number of cases at 165, or 48 percent of the U.S. total, followed by Florida with at least 38 calls to its poison center.

Dr. Rick Gellar, medical director for the California Poison Control System, said the first call about the substances came in Oct. 5, and a handful of calls have followed since. But he warned: "The only way this won't become a problem in California is if federal regulatory agencies get ahead of the curve. This is a brand new thing."

In the Midwest, the Missouri Poison Center at Cardinal Glennon Children's Medical Center received at least 12 calls in the first two weeks of January about teenagers and young adults abusing such chemicals, said Julie Weber, the center's director. The center received eight calls about the powders all of last year.

Dr. Richard Sanders, a general practitioner working in Covington, La., said his son, Dickie, snorted some of the bath salts and endured three days of intermittent delirium. Dickie Sanders missed major arteries when he cut his throat. As he continued to have visions, his physician father tried to calm him. But the elder Sanders said that as he slept, his son went into another room and shot himself.

"If you could see the contortions on his face. It just made him crazy," said Sanders. He added that the coroner's office confirmed the chemicals were detected in his son's blood and urine.

Sanders warns the bath salts are far more dangerous than some of their names imply.

"I think everybody is taking this extremely lightly. As much as we outlawed it in Louisiana, all these kids cross over to Mississippi and buy whatever they want," he said.

A small packet of the chemicals typically costs as little as \$20.

In northern Mississippi's Itawamba County, Sheriff Chris Dickinson said his office has handled about 30 encounters with bath salt users in the past two months alone. He said the problem grew last year in his rural area after a Mississippi law began restricting the sale of pseudoephedrine, a key ingredient in making methamphetamine.

Dickinson said most of the bath salt users there have been meth addicts and can be dangerous when using them.

"We had a deputy injured a week ago. They were fighting with a guy who thought they were two devils. That's what makes this drug so dangerous," he said.

But Dickinson said the chemicals are legal for now, leaving him no choice but to slap users with a charge of disorderly conduct, a misdemeanor.

Kentucky state lawmaker John Tilley said he's moving to block the drug's sale there, preparing a bill for consideration when his legislature convenes shortly. Angry that the powders can be bought legally, he said: "If my 12-year-old can go in a store and buy it, that concerns me."

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Merci.

L'Équipe de surveillance des médias
Santé Canada

MEPHEDRONE

Mephedrone is a synthetic derivative of cathinone, a naturally occurring compound found in the Eastern African plant Khat (*Catha edulis*). Mephedrone is a stimulant and is used as an alternative to amphetamines, cocaine, and MDMA (ecstasy). Mephedrone may be sold as capsules, tablets or white crystalline powder. The powder can be snorted, wrapped in cigarette paper and swallowed (“bombing”), or dissolved in liquid and injected. Mephedrone is often marketed as “plant food”, “bath salts”, or “research chemicals”.

Also Known As: Meph, drone, 4-MMC, MCAT, MMCAT, bubbles, Magic, meow, meow-meow, miaow, miaow-miaow, plant food, sub-coca, crab, methylamino, rush.

Category: Central Nervous System (CNS) stimulants

How Does Mephedrone Affect the Body?

Mephedrone is a stimulant and produces many of the same effects observed with amphetamines, cocaine or ecstasy such as increased alertness, a sense of well-being (“euphoria”), stimulation and feelings of excitement, increased openness/sociability and an urge to talk. Although relatively little information exists on the exact mechanism by which mephedrone affects the body, it probably raises the levels of “amine” neurotransmitters like dopamine, serotonin and norepinephrine in a manner resembling that of other stimulants. The effects of mephedrone are felt within 1-20 minutes after oral use, peaking at 45-60 minutes, with a come-down 1 to 2 hours after use. In some cases, the effects may persist for as long as 24 hours after exposure.

Will Mephedrone Always Produce the Same Effects?

The way a person feels after taking mephedrone may depend on many factors such as:

- age and weight
- mood, expectations and environment
- medical or psychiatric conditions
- the amount of mephedrone ingested (dose)
- how it is used
- how often and for how long mephedrone has been used
- use of other drugs including non-prescription, prescription, and street drugs

Short-Term Effects

Some of the short-term effects associated with mephedrone use include:

- euphoria, excitement, openness, chattiness
- rapid heart beat (tachycardia)
- chest pain

Annex B

- palpitations
- hypertension
- decreased blood circulation and painful white or blue extremities
- agitation, confusion, psychosis
- anxiety
- hallucinations
- enlarged pupils (mydriasis)
- tremor
- fever
- sweating
- nausea
- decreased appetite
- breathlessness
- dizziness
- headache
- skin rashes
- irritation/bleeding of the nose, mouth, or throat

Long-Term Effects

Very little is known about the long-term effects of using mephedrone. However, the effects are likely to be similar to those of other stimulants such as cocaine and amphetamines. These can include:

- depression
- mood swings
- restlessness
- insomnia
- erratic, bizarre or violent behaviour

Can Mephedrone Harm a Developing Fetus?

Very little is known about the effects of mephedrone on a developing fetus. However, mephedrone is related to cathinone, one of several sympathomimetic compounds found in the leaves of the Khat plant. There is some evidence that babies born to women who chewed Khat leaves during pregnancy had a lower birth weight. In addition, the consumption of sympathomimetic drugs such as cocaine or amphetamines during pregnancy has been linked to an increased risk of miscarriage, premature delivery, and decreased birth weight. These newborns were also more likely to be irritable, suffer from malnourishment, and suffer from disturbances in sleep within the first few weeks after birth.

Is Mephedrone Addictive?

It is not known if mephedrone is addictive. However, based on the fact that it produces many of the same psychological and physical effects as other addictive stimulants (cocaine, amphetamines), mephedrone is very likely to be addictive.



Fw: CBC.ca/health - Bath salt abuse brings 'horrible trip,' MD warns

Denis Arsenault to: Stephanie Chandler

2011-01-24 02:12 PM

History: This message has been replied to.

Denis

Denis Arsenault, A/Manager / Gestionnaire p.i.
Regulatory Policy Division /
Division des politiques réglementaires,
Office of Controlled Substances /
Bureau des substances contrôlées,
Health Canada / Santé Canada
Tel/Tél: (613) 957-6828
Fax / Télécopieur : (613) 946-4224
E-Mail/Courriel: denis_arsenault@hc-sc.gc.ca

----- Forwarded by Denis Arsenault/HC-SC/GC/CA on 2011-01-24 02:11 PM -----

From: Christine Roush/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC, Suzanne Desjardins/HC-SC/GC/CA@HWC
Cc: Denis Arsenault/HC-SC/GC/CA@HWC, Nicole Prentice/HC-SC/GC/CA@HWC
Date: 2011-01-24 02:05 PM
Subject: Fw: CBC.ca/health - Bath salt abuse brings 'horrible trip,' MD warns

Jocelyn - MO is asking for lines on this - and we found some in the database dating back to 2010. Can you please review and let me know if these are still OK. If so, then we will flip these to MO. thx.

Q1 - Mephedrone / cathinone: Is it legal? Health Quebec released statement yesterday - required hospitalization and intensive care due to drug; Is it a Schedule 3 controlled substance?

Mephedrone is a synthetic amphetamine-type stimulant also known as 4-methylmethcathinone. It is regulated as a controlled substance because it is an analog of amphetamine (specifically, 4-methylmethamphetamine), which is included in Schedule III to the Controlled Drugs and Substances Act. Mephedrone is illegal in Canada. Unless authorized by regulation, all activities with mephedrone, such as production, importation, exportation, possession, are prohibited in Canada.

Q2. Any health concerns reported?

A2. Relatively little scientific information exists regarding mephedrone (or 4-methylmethcathinone). However, mephedrone is an amphetamine and is therefore considered a stimulant. Amphetamines stimulate brain function resulting in increased wakefulness, alertness, euphoria and a sense of increased energy. Adverse effects can include seizures, cerebral hemorrhage, high fever, coma or death. Amphetamines also increase heart rate and blood pressure and untoward effects can include palpitations, irregular or abnormal heartbeat, heart attack, and cardiovascular collapse. People with underlying neurological, cardiac or psychological conditions, especially those on medication, are likely to be at greatest risk of serious adverse events. Co-abuse with other stimulant drugs or even alcohol may put the user at greater risk.

Q3. What's the departmental position on this?

A3. Mephedrone is a controlled substance under Schedule III of the Controlled Drugs and Substances Act. Unless authorized by regulation, production, importation, exportation, trafficking and possession of mephedrone is prohibited.

Christine Roush
Senior Communications Advisor/

From: Dave Stephens/HC-SC/GC/CA
To: christine.roush@hc-sc.gc.ca, nicole.prentice@hc-sc.gc.ca
Cc: alexis.m.tervo@hc-sc.gc.ca
Date: 2011-01-24 01:58 PM
Subject: Fw: CBC.ca/health - Bath salt abuse brings 'horrible trip,' MD warns

Christine, Nicole: please see below

Dave Stephens
Senior Communications Executive-Gestionnaire Principal des Communications
HECSB/DGSCSE
6th Floor, Room 6-033, 269 Laurier Ave. W., Ottawa, ON
Tel: (613) 946-8107
Cell: (613) 859-3581
----- Forwarded by Dave Stephens/HC-SC/GC/CA on 2011-01-24 01:58 PM -----

From: Alexis M Tervo/HC-SC/GC/CA
To: Dave Stephens/HC-SC/GC/CA@HWC
Date: 2011-01-24 01:57 PM
Subject: Re: Fw: CBC.ca/health - Bath salt abuse brings 'horrible trip,' MD warns

Hi Dave, MO is looking for lines on mephedrone. I found media responses from 2010 in the enquiry database. Are these still accurate? If so, I can flip these to MO and see if this is enough (or they may still want lines).

Q1 - Mephedrone / cathinone: Is it legal? Health Quebec released statement yesterday - required hospitalization and intensive care due to drug; Is it a Schedule 3 controlled substance?

Mephedrone is a synthetic amphetamine-type stimulant also known as 4-methylmethcathinone. It is regulated as a controlled substance because it is an analog of amphetamine (specifically, 4-methylmethamphetamine), which is included in Schedule III to the Controlled Drugs and Substances Act. Mephedrone is illegal in Canada. Unless authorized by regulation, all activities with mephedrone, such as production, importation, exportation, possession, are prohibited in Canada.

Q2. Any health concerns reported?

A2. Relatively little scientific information exists regarding mephedrone (or 4-methylmethcathinone). However, mephedrone is an amphetamine and is therefore considered a stimulant. Amphetamines stimulate brain function

resulting in increased wakefulness, alertness, euphoria and a sense of increased energy. Adverse effects can include seizures, cerebral hemorrhage, high fever, coma or death. Amphetamines also increase heart rate and blood pressure and untoward effects can include palpitations, irregular or abnormal heartbeat, heart attack, and cardiovascular collapse. People with underlying neurological, cardiac or psychological conditions, especially those on medication, are likely to be at greatest risk of serious adverse events. Co-abuse with other stimulant drugs or even alcohol may put the user at greater risk.

Q3. What's the departmental position on this?

A3. Mephedrone is a controlled substance under Schedule III of the Controlled Drugs and Substances Act. Unless authorized by regulation, production, importation, exportation, trafficking and possession of mephedrone is prohibited.

Alexis Tervo
Communications Advisor
Public Affairs, Communications and Consultation
Health Canada
Ph: (613) 286-5487

Fw: CBC.ca/health - Bath salt abuse brings 'horrible trip' MD warns

Clarke Olsen
to:
Heidi Jackson
2011-01-24 01:45 PM

Cc:
Martina Vorel, graham.howell, Jenny VanAlstyne, Alexis M Tervo, tim.vail,
Stephanie Priest

Hello Heidi,

Can we please get some quick info about the story below for end of day.

What is the status of MDPV in Canada, and would bath products containing it be legal? Is the regulatory status of Mephedrone accurately reported below? My quick scan of the act didn't find it explicitly listed in schedule 3. I've also copied Stephanie in case there is a therapeutic angle to any of this.

Alexis, can we please have some lines drafted once we receive the above information.

Thanks,



Reuters.com - Senator moves to ban drug sold under bath salts guise

HC_Media_SC to:

2011-01-31 09:01 AM

Sent by: Hisham Kelati

Rec: Denis Arsenault

Distribution group/Groupe de distribution: Pharmaceuticals Biologics and Genetic Therapies -
HPFB/DGPSA, Consumer Product Safety - Sécurité des produits de consommation - HECSB/DGSESC,
Controlled Substances - Substances contrôlées - HECSB/DGSESC,

Reuters.com

Senator moves to ban drug sold under bath salts guise

<http://www.reuters.com/article/2011/01/30/us-drugs-bathsalts-idUSTRE70T3PR20110130>

(Reuters) - Two drugs that produce a "meth-like" high and are being sold under the guise of "bath salts" would be banned as federally controlled substances under a bill unveiled on Sunday by Senator Charles Schumer.

"These so-called bath salts contain ingredients that are nothing more than legally sanctioned narcotics, and they are being sold cheaply to all comers, with no questions asked, at store counters around the country," said Schumer, a New York Democrat.

Schumer said he will introduce a bill to outlaw the two synthetic drugs -- mephedrone and methylenedioxypyrovalerone, or MDPV. The drugs come in powder and tablet form and are ingested by snorting, injection, smoking and, less often, by use of an atomizer.

Users experience an intense high, euphoria, extreme energy, hallucinations, insomnia and are easily provoked to anger, according to the Drug Enforcement Administration, which is currently investigating the drugs.

They have emerged as legal alternatives to cocaine and methamphetamines, and one or both have already been banned in the European Union, Australia, Canada, and Israel. In the United States, Florida, Louisiana and North Dakota have all recently banned the substances.

"The longer we wait to ban the substance, the greater risk we put our kids in," Schumer said.

Media reports over the last year describe the drugs as becoming increasingly popular, particularly among young people attending nightclubs, although the actual number of individuals using the drugs is unknown.

"These products are readily available at convenience stores, discount tobacco outlets, gas stations, pawnshops, tattoo parlors, truck stops and other locations," said an alert issued by the DEA.

"Prices range from \$25 to \$50 per 50-milligram packet," the DEA alert said.

The European Union banned mephedrone in December, saying the drug was directly linked to the deaths of two people, and may have been tied to 37 other cases of death.

The European Union's report said there was limited scientific evidence on the effects of the drug -- believed to be mostly manufactured in Asia before being packaged in the West -- but that there was sufficient evidence of its health risks to support a ban.

Schumer has also asked the health commissioner of New York State, Nirav Shah, to ban the two substances.

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6

PUBLICATION: GLOBE AND MAIL
IDN: 110310066
DATE: 2011.01.31
PAGE: L3
BYLINE: ZOSIA BIELSKI
SECTION: ~~Globe Life~~
EDITION: Metro
DATELINE:
WORDS: 741
WORD COUNT: 745
CIRCULATION: 321109

not "Real Bath salts"
(epson)
HCl / My son

SUBSTANCE ABUSE Powerful 'bath salt' drugs quickly gain cult following Sales of extremely addictive, meth-like powder fanned out across the U.S. through unregulated online sales

ZOSIA BIELSKI An epidemic of "bath salt" abuse is sweeping the United States and some experts worry that it may hit Canada, since the designer drugs are unregulated and available on the Web.

→ Not actually bath salts, the products labelled Red Dove, Ivory Wave and Hurricane Charlie are also available via small retail outlets to customers who smoke, snort, inject or eat the chemicals.

The powders' effects are similar to those of methamphetamine, and can include rapid heart rate, visual hallucinations, paranoia and psychosis, as well as self-mutilation and suicidal thoughts, authorities say.

A man from Fulton, Miss., cut his face and stomach repeatedly after hallucinating on the drugs. In Louisiana, the family of a 21-year-old man says he committed suicide following three days of delirium after he snorted the chemicals, according to the Washington Post.

Since September, poison-control centres from California to Florida have received hundreds of calls about exposure to mephedrone and methylenedioxypropylvalerone (MDPV), the substances in the powders.

The first calls appeared in Louisiana, which outlawed the salts with an emergency order in January, after the state's poison centre got more than 125 calls between October and

December.

Although most victims have been men 25 to 35 with a history of meth abuse, authorities are sounding the alarm for younger users curious to experiment.

"One of the risks that you take with this is killing yourself or hurting someone else," said Richard Geller, medical director of the California Poison Control System.

"If a college student is to engage in this behaviour, they need to know that this is unusually high risk. You'd have to be unbelievably foolish to try this if you knew about it." The California centre has received six emergency calls from people who used the drugs. All of the calls came from different parts of the state, which suggests to Dr. Geller that Californians are buying the salts online.

"We live in a rapid-cycle, fast-transportation era. It's no surprise that things spread this quickly any more," he said.

"Drug abuse knows no borders. The U.S.-Canadian border, even after 9/11, is porous. What shows up here will find its way to Toronto." Authorities believe the substances may come into the United States through the Port of New Orleans via ships from India and China.

Head shops and convenience stores also sell the salts, often in containers marked "not for human consumption." A 250-milligram jar or baggie goes for \$25 (U.S.).

Occasionally, the drug is marketed as plant food, as it was in the U.K. when that country saw an epidemic earlier last summer.

"If you really wanted bath salts, you wouldn't buy this because the quantity is so small," Dr. Geller said. "You're not going to find it at Bed Bath & Beyond." American companies are starting to distance themselves from the stimulants, including The San Francisco Bath Salt Company, which issued a terse statement last week.

"These are not your typical bath salts, or really even bath salts at all," wrote a representative, adding that none of the imposters contain sodium chloride (sea salt) or magnesium sulfate (epsom salt), "staple ingredients of a typical and true bath salt." Although not yet regulated, the powders are now facing federal scrutiny in the U.S., with lawmakers in Kentucky and Mississippi now looking to ban their sale.

Although officials at Health Canada are aware of the drugs, they have not seen widespread marketing or use of the products in this country.

"In 2010, only seven seizures of drugs analyzed by Health Canada's Drug Analysis Service were found to contain MDPV. This indicates that this substance is not seen very often in Canada," spokesman Stephane Shank wrote in an e-mail, adding that the agency will monitor the products.

"We're not seeing the bath salts coming into our service," said Michael Torres of media relations with the Centre for Addiction and Mental Health.

Still, Dr. Geller says the salts are enjoying a hugely lucrative trade in the U.S., which is worrying since they have the "worst possible aspects of a number of drugs." "There's visual hallucinations like LSD, only they're worse than LSD because they motivate violent behaviour," Dr. Geller says.

"It seems to create a dependence and craving immediately, worse than crack cocaine. It has created psychotic breaks and some of these people are not getting better."

ADDED SEARCH TERMS:

GEOGRAPHIC NAME: United States

SUBJECT TERM: bath salts; drug abuse; illegal drugs; poisoning; public health; regulation

Updated: 2002-08-15

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Meow Meow - otherwise known as Bath Salts
Christine Roush to: Jocelyn Kula
Cc: Stephanie Szick, Denis Arsenault, Stephanie Chandler

2011-02-17 11:02 AM

FYI - another article of interest to CSTD in today's clips.

PUBLICATION: GLOBE AND

MAIL

IDN: 110480069
DATE: 2011.02.17
PAGE: A7
BYLINE: PATRICK WHITE
SECTION: National News
EDITION: Metro
DATELINE:
WORDS: 473
WORD COUNT: 480

CIRCULATION: 321109

**CRIME Police warn of rise of mephedrone after GTA
bust Popular drug with British club-goers, also known as
meow-meow, already discovered in Newfoundland and
Quebec**

PATRICK WHITE The drug is called meow-meow and British club-goers have taken to it like a kitty to cat-nip, hospitalizing dozens and leaving lawmakers scrambling to legislate it out of existence.

Now it's Canada's turn.

On Tuesday, a drug bust conducted throughout the Greater Toronto Area netted four kilos of mephedrone, the main culprit in England's recent legislative drug war. Authorities here were so unfamiliar with the narcotic, an off-white powder often marketed as plant food or bath salts to circumvent European trafficking laws, that no one knew exactly what it was when drug officers stumbled upon the stash during an early morning raid.

"This was the first time we'd seen it," Durham Regional Police Inspector Dave Wilson said. "I can only compare it to 1991, when we made our first seizure of crack cocaine." The drug - known by the street names meow-meow, MCAT, bubbles and drone - has appeared in small quantities in Newfoundland and Quebec. In all, **Health Canada** has identified just five

samples from drug busts across the country. But the recent seizure could signal an escalation in efforts to push the club drug on Canadian streets.

"Is it readily available out there or is this the first shipment and we just got lucky? I'm not sure," said Inspector Tim Farquharson, of Peterborough Lakefield police, another agency involved in the bust. "We already have enough problems with crack and OxyContin here." In Britain, mephedrone filled a void created by the rapidly declining quality of cocaine and ecstasy. Users were drawn to the drug on the promise of a brief but intense euphoria.

What's more, it was cheap, costing half the price of the \$60 an ounce that Britons were dropping on adulterated cocaine. "It proved very attractive for disillusioned cocaine users," said Allen Morgan, a prominent expert witness in British drug trafficking cases. But its most appealing quality had to be its ambiguous legal status.

"There were no controls and the police were unable to take any action," Mr. Morgan said. "Essentially the drug was legal, clean and unadulterated and it took off. There hasn't been a drug for a long time that has become so publicly prominent." Head shops began selling mephedrone over the counter and online.

But serious health effects began emerging in late 2009 and 2010, with dozens of mephedrone users admitted to emergency rooms complaining of heart palpitations, anxiety, nausea, hypertension and vomiting.

The British Parliament finally banned it in April of last year after media reports linking mephedrone to several deaths. As an analogue of amphetamine, in Canada mephedrone is a Schedule 3 controlled substance. The Toronto-area bust - which included seizures of cocaine, marijuana and hashish - led to 19 arrests on 115 charges. The street value of the mephedrone was pegged at around \$350,000.

ADDED SEARCH TERMS:

GEOGRAPHIC NAME: Canada; Toronto

SUBJECT TERM: drug charges; illegal drugs; mephedrone

Updated: 2002-08-15



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Christine Roush
Senior Communications Advisor/
Conseillère principale en communications
Public Affairs, Consultation and Communications Branch/
Direction générale des affaires publiques,
de la consultation et des communications
Health Canada/Santé Canada
Tel/Tél : (613) 954-0712/Cell: (613) 219-7194

Fax/Facsimile : 948-8085
E-mail / courriel : christine_roush@hc-sc.gc.ca

Drafted by N. Isiche
March 31, 2011
3:22pm

#11-002321-409

s.19(1)

re: *Hallucinogenic "Bath salts"*

Dear [REDACTED]

Thank you, for your correspondence of 2011-03-21 expressing your serious concerns on "bath salts", a topic of discussion of a recent episode of the popular U.S. "Dr. Oz" show which aired on 2011-03-24.

As you are aware, these products are not actually traditional bath salts or epsom salts of magnesium sulphate. They are dangerous products containing methylenedioxypropylone (MDPV) and mephedrone synthetic chemicals.

In regards to your enquiry on current actions to make "bath salts" illegal in Canada, despite MDPV sharing a basic structural element with several controlled substances (cathinone, methcathinone, diethylpropion, phenmetrazine and pyrovalerone), based on current information available to the Office of Controlled Substances, it appears that MDPV is not considered a ✓ controlled substance under the schedules of the *Controlled Drugs and Substances Act* (CDSA).

As for mephedrone is a synonym for 4-methylmethcathinone which is analogous to 4-methylmethamphetamine and is included in item 1 of Schedule III to the CDSA. Consequently, mephedrone is considered a controlled substance under the CDSA and its sale, production, importation, exportation, trafficking and possession is prohibited unless authorized under the CDSA or its regulations.

MDPV is generally compared with amphetamines and other stimulants. Abuse of MDPV and mephedrone have known to result in such effects as paranoia, rapid heart rates, terrifying hallucinations, violent behavior including self-infliction of bodily harm, suicidal thoughts and tendencies, long-term psychological effects and death. As stimulants affect neurotransmitters in the brain, intense cravings for the drug also result in drug dependence. These products are commonly in powdered form and abused by ingestion, smoking, snorting, injection or rectal administration.

In the U.S., these stimulants are not yet regulated by the U.S. Drug Enforcement Administration. In the State of Louisiana, "bath salts" were outlawed by an emergency order following receipt of 125 calls in a three-month period to the State's Poison Control Centre. Other States are considering similar regulatory actions.

"Bath salt" products have been extensively marketed on the Internet under various brand names including; Blue Silk, Charge+, Ivory Snow, Uncle Charlie, Ivory Wave, Ocean Burst, Pure Ivory, Purple Wave, Super Coke, Stardust, Vanilla Sky, Red Dove, White Dove, White Knight and White Lightening.

Based on Canadian surveillance monitoring data, the high degree of abuse seen in the U.S. has not yet arisen here in Canada. In 2010, only seven(7) seizures of drugs analysed by Health Canada's Drug Analysis Service were found to contain MDPV suggesting that Canadian usage is not as widespread as in the United States.

Health Canada shares your serious concerns over the widespread availability to these ~~dangerous synthetics, especially youth's access to these dangerous products of high abuse~~ potential and acknowledge the very serious and life-threatening health risks they pose to Canadians, especially our vulnerable youth.

Current on-going market surveillance and policing activities by Government and law enforcement agencies in Canada for "bath salts, MDPV and mephedrone" will assist in monitoring of any escalation product marketing, abuse, diversion and trafficking in Canada.

These activities will also result in the enforcement of Canadian law to the greatest extent possible until such time as the CDSA and its regulations can be amended to include MDPV.

Cathy A. Sabiston
Director General
Controlled Substances and Tobacco Directorate
Healthy Environments and Consumer Safety Branch
Health Canada

cc. Tweed, Merv - M.P.
Brandon-Souris

16



Re: Fw: mephedrone 
Evelyn Soo to: Nathan J Isotalo

2011-03-31 04:11 PM

Hi Nathan

As discussed, I am attaching a copy of the status report for mephedrone. I have to update my database but will forward a copy along to you as well as a link to the L:\ drive to facilitate your future searches.

Thanks for your patience.

Evelyn



C-4-Methylmethcathinone_mephedrone.wpd

Evelyn C Soo, PhD
A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
environnementale et de la sécurité des consommateurs (DGSESC)
Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
evelyn.soo@hc-sc.gc.ca
Telephone | Téléphone 613-954-1758
Government of Canada | Gouvernement du Canada

Nathan J Isotalo

Thank you, Evelyn...do you have one for mephe...

2011-03-31 09:30:27 AM

From: Nathan J Isotalo/HC-SC/GC/CA
To: Evelyn Soo/HC-SC/GC/CA@HWC
Date: 2011-03-31 09:30 AM
Subject: Fw: mephedrone

Thank you, Evelyn...do you have one for mephedrone also? My understanding is that mephedrone is an analogue of cathinone and is thus considered scheduled. Nathan.

Mr. Nathan Isotalo
Sr. Policy Analyst
Regulatory Policy Division
Office of Controlled Substances
Controlled Substances Tobacco Directorate
HECS Health Canada
Tel. (613) 946-4225

----- Forwarded by Nathan J Isotalo/HC-SC/GC/CA on 2011-03-31 09:25 AM -----

From: Evelyn Soo/HC-SC/GC/CA
To: Nathan J Isotalo/HC-SC/GC/CA@HWC
Date: 2011-03-30 09:04 PM
Subject: Re:

000128

Hi Nathan

As requested, please find the status report for MDPV.

Best wishes
Evelyn

[attachment "NC-3',4'-Methylenedioxy-alpha-pyrrolidinopentanophenone (MDPV) 2006-06-27.wpd"
deleted by Nathan J Isotalo/HC-SC/GC/CA]

Evelyn C Soo, PhD
A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
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Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
evelyn.soo@hc-sc.gc.ca
Telephone | Téléphone 613-954-1758
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Nathan J Isotalo

Hi Evelyn do you still handle the status reports.....

2011-03-30 04:12:28 PM

Drug Status Report

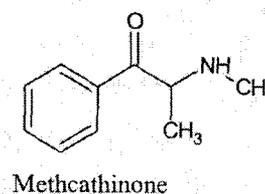
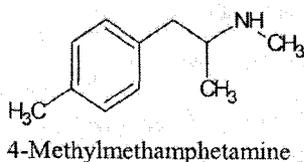
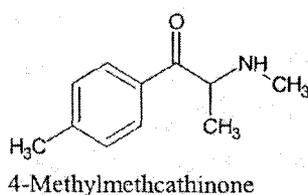
Drug: 4-Methylmethcathinone

Drug Name Status: 4-Methylmethcathinone is the common name

Other Names: Mephedrone; 2-methylamino-1-p-tolylpropan-1-one

Chemical Name: 2-Methylamino-1-(4-methylphenyl)-1-propanone

Chemical structure:



Molecular Formula: C₁₁H₁₅NO

Pharmacological class / Application: stimulant

International status:

US: The substance is not currently listed on the US Controlled Substances Act and is not mentioned on the DEA website. However, 4-methylmethcathinone is controlled¹ in the US due to the analogue provisions in the CSA.

United Nations: The substance is not listed on the Yellow List - List of Narcotic Drugs under International Control nor the Green List - List of Psychotropic Substances under International Control.

Canadian Status: Item 1 of Schedule III to the CDSA is, "Amphetamines, their salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues." Although not listed specifically in item 1 of Schedule III, 4-methylmethamphetamine (structure above) is an amphetamine. 4-Methylmethcathinone is analogous to 4-methylmethamphetamine in that it contains the same structure with an additional oxygen. 4-Methylmethcathinone is therefore an analogue of 4-methylmethamphetamine and is included in item 1 of Schedule III to the CDSA.

A similar rationale was used to recommend that 2-methylamino-1-(3,4-methylenedioxy)-propiophenone be included in item 1 of Schedule III. That report is appended for information.

¹ http://www.usdoj.gov/dea/programs/forensicsci/microgram/journal_v5_num14/pg1.html

The substance is also structurally similar to 2-methylamino-1-phenyl-1-propanone (methcathinone) which is listed as item 21 of Schedule III to the CDSA.

Recommendation: 4-Methylmethcathinone is included in item 1 of Schedule III to the CDSA and is a controlled substance.

June 19, 2008

Club drug mephedrone faces ban in U.K.

Last Updated: Monday, March 29, 2010 | 3:45 PM ET

CBC News

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Beginning of Story Content

Mephedrone, a legal drug linked to several deaths last year in Britain, will be criminalized, a government official says.

The U.K. government's panel of scientific experts recommended restrictions on mephedrone, a synthetic drug also known as M-Cat and Meow-Meow. The drug can be bought over the internet and is popular in nightclubs.

The Advisory Council on the Misuse of Drugs recommended classifying mephedrone as a Class B controlled substance. This class includes cannabis and amphetamines. Possession carries a maximum sentence of five years in jail, while supplying it carries a penalty of up to 14 years, according to the Home Office.

The European Monitoring Center for Drugs and Drug Addiction said more than 30 web sites promote the substance, which often originates in Chinese labs. A single dose costs about \$4.50 US, according to public health researchers.

Mephedrone is a synthetic form of cathinone, the active ingredient in khat, which is a stimulant popular in parts of Africa, said Steven Grant, chief of the clinical neuroscience branch at the U.S. National Institute on Drug Abuse.

"As a result of the council's advice, I'm introducing legislation to ban not just mephedrone and other cathinones but also to enshrine in law a generic definition ... so that we can be in the forefront of dealing with this whole family of drugs," Home Secretary Alan Johnson told reporters Monday.

"This will stop unscrupulous manufacturers and others peddling different but similar harmful drugs."

Khat, which is often chewed or brewed into tea, is chemically and pharmacologically similar to amphetamines and cocaine, Grant said.

"With mephedrone, you are taking a purified drug in pill form so unlike tea made out of khat, you're taking substantially more," Grant said. It has no known medicinal use, he added.

Drug prohibited in Canada

Mephedrone grabbed headlines in Britain after the deaths of Louis Wainwright, 18, and his 19-year-old friend Nicholas Smith earlier this month.

In Canada, mephedrone is a controlled substance under Schedule III of the Controlled Drugs and Substances Act.

Production, importation, exportation, trafficking and possession of mephedrone is prohibited unless

authorized by regulation, Health Canada said in an email to CBC News Monday.

There is relatively little scientific information on the amphetamine mephedrone or 4-methylmethcathinone, the department noted.

"Amphetamines also increase heart rate and blood pressure, and untoward effects can include palpitations, irregular or abnormal heartbeat, heart attack, and cardiovascular collapse," Health Canada warned.

"People with underlying neurological, cardiac or psychological conditions, especially those on medication, are likely to be at greatest risk of serious adverse events. Co-abuse with other stimulant drugs or even alcohol may put the user at greater risk."

Health Canada's drug analysis service has received few exhibits of mephedrone from police.

Elsewhere in Europe, Sweden, Germany, and the Netherlands have made mephedrone illegal.

In the U.K., Johnson said he is determined not only to ban mephedrone but also close legal loopholes that allow similar compounds to slip through.

"I've instructed the U.K. Border Agency to seize and destroy shipments of these drugs at our borders, and shops and websites that are supplying the drug ... will be warned that they will very soon on the wrong side of the law," Johnson said.

In the U.S., mephedrone is not illegal, and the low level of usage means it's not a priority, the Associated Press reported.

With files from The Associated Press

End of Story Content

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End of Story Social Media

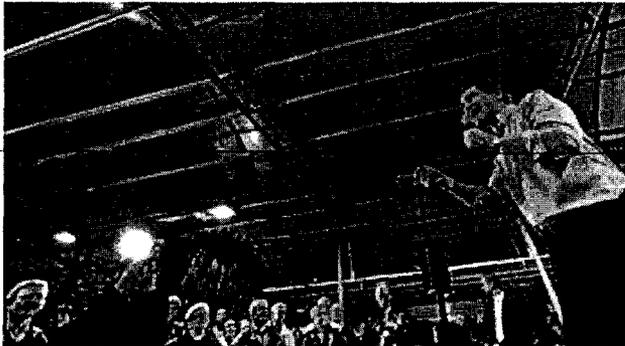
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19



Fw: CBC.ca/health - Fake marijuana causes U.S. poisoning surge

Jocelyn Kula to: Nathan J Isotalo, Denis Arsenault

2011-04-06 11:09 AM

for the mephedrone and spice files pls

↳ Bath salt (Mephedrone + MDPV)
↳ Edible + Herbal Incense

Jocelyn Kula

Acting Director/ Directrice par intérim

Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada/ Santé Canada

Tel: (613) 952-2177 Fax: (613) 946-4224

----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2011-04-06 11:09 AM -----

From: HC_Media_SC/HC-SC/GC/CA

To:

Date: 2011-04-06 10:59 AM

Subject: CBC.ca/health - Fake marijuana causes U.S. poisoning surge

Sent by: Hisham Kelati

Distribution group/Groupe de distribution: Controlled Substances - Substances contrôlées - HECSB/DGSESC,

CBC.ca/health

Fake marijuana causes U.S. poisoning surge

<<http://www.cbc.ca/news/health/story/2011/04/06/us-synthetic-drugs.html>>

Synthetic substances that mimic marijuana, cocaine and other illegal drugs are making users across the United States seriously ill, according to the American Association of Poison Control Centers.

The products are often packaged as incense or bath salts and can be obtained for as little as \$10 at many head shops, but they are causing seizures and hallucinations and even killing some people.

At the request of The Associated Press, the poison control association analyzed nationwide figures on calls related to synthetic drugs. The findings showed a sharp increase in the number of people seeking medical attention.

At least 2,700 people have fallen ill since January, compared with fewer than 3,200 cases in all of 2010. At that pace, medical emergencies related to synthetic drugs could go up nearly fivefold by the end of the year.

"Many of the users describe extreme paranoia," said Dr. Mark Ryan, director of the Louisiana Poison Center. "The recurring theme is monsters, demons and aliens. A lot of them had suicidal thoughts."

The chemicals are suspected in at least nine U.S. deaths since last year, including that of Mike Rozga's 18-year-old son, David, an athlete and band standout from Indianola.

The young man got high last June on a marijuana look-alike product called "K2" and complained to a friend "that he felt like he was in hell," his father said.

Though the teen had never suffered from depression, he went home, found a shotgun and killed himself.

"These kids weren't looking for anything bad to happen," Mike Rozga said. "The truth is they didn't know what they had gotten themselves into."

The recent surge in activity has not gone unnoticed by authorities. The Drug Enforcement Administration recently used emergency powers to outlaw five chemicals found in synthetic pot, placing them in the same category as heroin and cocaine.

But manufacturers are quick to adapt, often cranking out new formulas that are only a single molecule apart from the illegal ones.

Recreational drugs created in the laboratory have been around at least since the middle of the 20th century, when LSD was first studied. But these latest examples emerged only a few years ago, starting in Europe.

The products were typically made in China, India and other Asian nations and soon arrived in Britain and Germany, according to DEA spokesman Rusty Payne.

In the United States, fake marijuana was last year's big seller, marketed under brands such as "K2" or "Spice." This year, the trend is "bath salts" with names like "Purple Wave" and "Bliss."

Besides being cheap and easily obtained, they do not show up in common drug tests.

Synthetic marijuana typically involves dried plant material sprayed with one of several chemical compounds, most of which were created by a Clemson University scientist for research purposes in the 1990s. The compounds were never tested on humans.

It's packaged to look like pot, and users typically smoke it, but experts say the high is more comparable to cocaine or LSD.

The bath salts are not water-softening products at all but crystalized chemicals that are snorted, swallowed or smoked. They contain two powerful stimulants: methylenedioxypropylamphetamine (or MDPV) and mephedrone, which mimic cocaine, LSD and methamphetamine.

So far in 2011, poison control centers have received nearly 1,300 calls about synthetic pot, compared with 2,874 calls for all of last year, according to the poison control center data.

Poison calls for bath salts rose at an even greater rate. The centers took 301 calls in all of 2010, but had more than 1,400 for the first three months of 2011. Most of the calls came from doctors and nurses reporting patients in emergency rooms.

"The problem is really exploding here," said Dr. Elizabeth Scharman, director of the West Virginia Poison Center. Her state had three cases of bath-salt poisoning in December.

"We've had 131 cases since Jan. 1," and one-third of those were within the past two weeks, she said late last month. A law banning bath salts and synthetic marijuana was signed Tuesday by acting Gov. Earl Ray Tomblin.

"One described it as like being on cocaine, but 10 times worse," said Anna Rouse Dulaney of the Carolinas Poison Center in Charlotte, N.C.

DEA agent Gary Boggs said users assume that the products are safe because they are available in stores, even though they are typically labeled "not for human consumption."

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L'Équipe de surveillance des médias
Santé Canada

Fake marijuana causes U.S. poisoning surge

The Associated Press

Posted: Apr 6, 2011 7:57 AM ET

Last Updated: Apr 6, 2011 9:01 AM ET

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Beginning of Story Content

Synthetic substances that mimic marijuana, cocaine and other illegal drugs are making users across the United States seriously ill, according to the American Association of Poison Control Centers.



Containers of bath salts, a synthetic cocaine, sit on a counter at Hemp's Above in Mechanicsburg, Pa. Synthetic substances that mimic marijuana, cocaine are causing seizures and hallucinations so intense that thousands of them seek help in U.S. emergency rooms. Chris Knight/The Patriot-News/Associated Press

The products are often packaged as incense or bath salts and can be obtained for as little as \$10 at many head shops, but they are causing seizures and hallucinations and even killing some people.

At the request of The Associated Press, the poison control association analyzed nationwide figures on calls related to synthetic drugs. The findings showed a sharp increase in the number of people seeking medical attention.

At least 2,700 people have fallen ill since January, compared with fewer than 3,200 cases in all of 2010. At that pace, medical emergencies related to synthetic drugs could go up nearly fivefold by the end of the year.

"Many of the users describe extreme paranoia," said Dr. Mark Ryan, director of the Louisiana Poison Center. "The recurring theme is monsters, demons and aliens. A lot of them had suicidal thoughts."

The chemicals are suspected in at least nine U.S. deaths since last year, including that of Mike Rozga's 18-year-old son, David, an athlete and band standout from Indianola.

Death blamed on marijuana lookalike

The young man got high last June on a marijuana look-alike product called "K2" and complained to a friend "that he felt like he was in hell," his father said.

Though the teen had never suffered from depression, he went home, found a shotgun and killed himself.

"These kids weren't looking for anything bad to happen," Mike Rozga said. "The truth is they didn't know what they had gotten themselves into."

The recent surge in activity has not gone unnoticed by authorities. The Drug Enforcement Administration recently used emergency powers to outlaw five chemicals found in synthetic pot, placing them in the same category as heroin and cocaine.

But manufacturers are quick to adapt, often cranking out new formulas that are only a single molecule apart from the illegal ones.

Recreational drugs created in the laboratory have been around at least since the middle of the 20th century, when LSD was first studied. But these latest examples emerged only a few years ago, starting in Europe.

Drugs made in China, India

The products were typically made in China, India and other Asian nations and soon arrived in Britain and Germany, according to DEA spokesman Rusty Payne.

In the United States, fake marijuana was last year's big seller, marketed under brands such as "K2" or "Spice." This year, the trend is "bath salts" with names like "Purple Wave" and "Bliss."

Besides being cheap and easily obtained, they do not show up in common drug tests.

Synthetic marijuana typically involves dried plant material sprayed with one of several chemical compounds, most of which were created by a Clemson University scientist for research purposes in the 1990s. The compounds were never tested on humans.

It's packaged to look like pot, and users typically smoke it, but experts say the high is more comparable to cocaine or LSD.

The bath salts are not water-softening products at all but crystalized chemicals that are snorted, swallowed or smoked. They contain two powerful stimulants: methylenedioxypyrovalerone (or MDPV) and mephedrone, which mimic cocaine, LSD and methamphetamine.

Poison control calls rise sharply

So far in 2011, poison control centers have received nearly 1,300 calls about synthetic pot, compared with 2,874 calls for all of last year, according to the poison control center data.

Poison calls for bath salts rose at an even greater rate. The centers took 301 calls in all of 2010, but had more than 1,400 for the first three months of 2011. Most of the calls came from doctors and nurses reporting patients in emergency rooms.

"The problem is really exploding here," said Dr. Elizabeth Scharman, director of the West Virginia Poison Center. Her state had three cases of bath-salt poisoning in December.

"We've had 131 cases since Jan. 1," and one-third of those were within the past two weeks, she said late last month. A law banning bath salts and synthetic marijuana was signed Tuesday by acting Gov. Earl Ray Tomblin.

→ West Virginia .

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"One described it as like being on cocaine, but 10 times worse," said Anna Rouse Dulaney of the Carolinas Poison Center in Charlotte, N.C.

DEA agent Gary Boggs said users assume that the products are safe because they are available in stores, even though they are typically labeled "not for human consumption."

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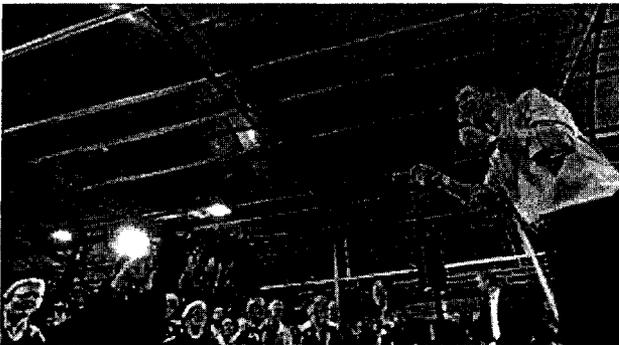
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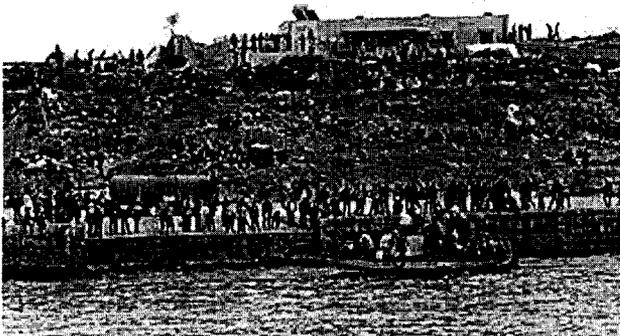
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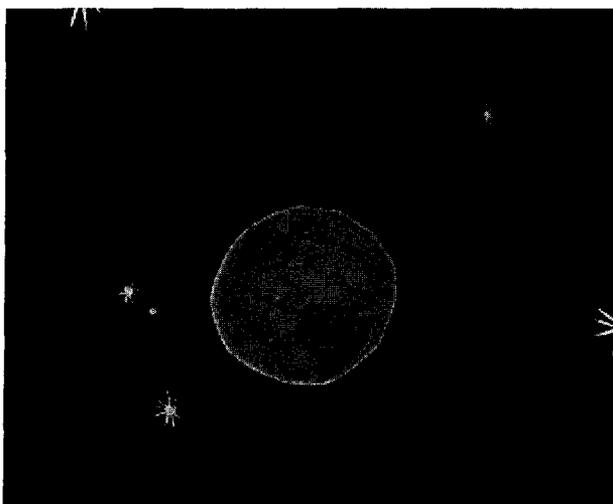
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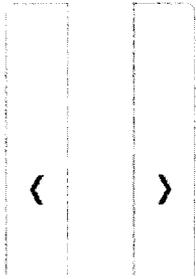
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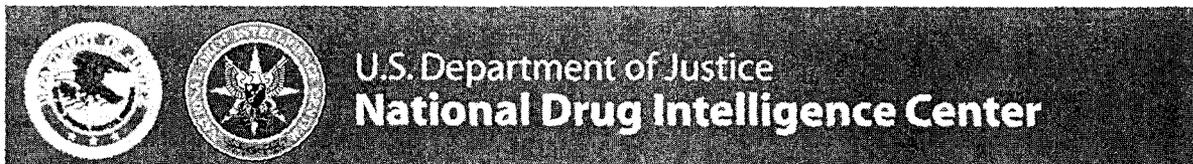


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July 2011

Situation Report

Product Number 2011-S0787-004

Synthetic Cathinones (Bath Salts): An Emerging Domestic Threat



Cox Broadcasting

Executive Summary

The National Drug Intelligence Center (NDIC) assesses with high confidence that the distribution and abuse of synthetic cathinones will increase in the United States in the near term, posing yet another challenge to U.S. law enforcement officials. Poison control centers and medical professionals around the country are increasingly reporting patients suffering adverse physical effects associated with abuse of these drugs, further compounding the problem.

Available data and law enforcement reporting suggest increasing levels of synthetic cathinone availability and abuse, but such information is limited and precise levels are unknown. U.S. Customs and Border Protection (CBP) currently tracks seizures of synthetic cathinones at U.S. ports of entry (POEs), but many synthetic cathinone products are disguised or mislabeled to impede detection. Because common field test kits, drug-detecting canines, and routine urine drug screens do not detect synthetic cathinones, law enforcement officials are challenged in interdicting such drugs and prosecuting their manufacturers and distributors.

Synthetic Cathinones (Bath Salts): An Emerging Domestic Threat

Synthetic cathinones, typically marketed as “bath salts” and “plant food,” are sold legally under various names (Ivory Wave, Blizzard, etc.) in most areas of the United States. The products are generally sold in retail establishments such as adult stores, independently owned convenience stores, gas stations, head shops, and skateboard shops. The products, as well as their raw chemical components, are also sold on many Internet sites, including popular Internet auction sites. Additionally, synthetic cathinones have been sold by independent dealers as ecstasy^a—in powdered form, in single-component tablets and capsules, and in tablets and capsules containing cathinones combined with MDMA (3,4-methylenedioxymethamphetamine) or other illicit controlled substances. Abusers typically ingest, inhale, inject, smoke, or snort (insufflate) the drugs to experience stimulant effects similar to those induced by amphetamine.

Manufacturers and distributors of synthetic cathinone products evade U.S. Drug Enforcement Administration (DEA) regulation and enforcement because synthetic cathinones are not scheduled under the Federal Controlled Substances Act (CSA). However, possession and distribution of the synthetic cathinones may be prosecuted, albeit with greater difficulty, under the Federal Controlled Substance Analogue Enforcement Act of 1986 (as amended)^b of the CSA. The availability and suitability of a prosecution under the analogue statute depends on the particular compound being trafficked and the facts of the case. Further, distributors deceptively market synthetic cathinone products as “not for human consumption” to evade U.S. Food and Drug Administration (FDA) scrutiny. Cathinone products that are introduced into interstate commerce and promoted as alternatives to illicit street drugs may be prosecutable under the Federal Food, Drug, and Cosmetic Act as unapproved new drugs and misbranded drugs. (See the offenses at 21 U.S.C. 331(a), (d) and penalties at 21 U.S.C. 333.)¹ Additionally, members of the Congress have introduced legislation to nationally ban the sale of certain synthetic cathinones,^c and, as of April 2011, all 50 states and the District of Columbia have introduced or announced plans to introduce legislation banning or restricting the distribution and possession of certain synthetic cathinones and cathinone derivatives. As synthetic cathinones become more regulated, abusers will likely use the Internet with greater frequency to purchase cathinone products, the raw chemicals used in their production, and products that contain cathinones not specifically prohibited by enacted legislation.

-
- a. Ecstasy tablets typically contain MDMA (3,4-methylenedioxymethamphetamine) but can contain various other drugs in place of or in combination with MDMA. Other drugs commonly identified in ecstasy include methamphetamine, amphetamine, BZP (N-benzylpiperazine), and caffeine.
- b. The Federal Controlled Substance Analogue Enforcement Act, enacted in 1986 as Pub. L. 99-570, title I, subtitle E, provides: “[a] controlled substance analogue shall, to the extent intended for human consumption, be treated . . . as a controlled substance in Schedule I.” The term “controlled substance analogue” is defined as a substance: (i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II; (ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or (iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II.”
- c. S. 409, the “Combating Dangerous Synthetic Stimulants Act of 2011”.

Product Number 2011-S0787-004

National Drug Intelligence Center

Background

Synthetic cathinones are central nervous system stimulants. They are chemically similar to cathinone, a Schedule I controlled substance that occurs naturally in the khat² plant (*Catha edulis*). The category of synthetic cathinones includes a number of drugs, such as MDPV (3,4-methylenedioxypropylone) and mephedrone (which have been identified by the FDA Office of Criminal Investigations in illicit "bath salt" products;³ see Appendix A) as well as *N*-methylcathinone (also known as methcathinone or cat),⁴ 4-fluoromethcathinone (also known as flephedrone or 4-FMC),⁵ and 3,4-methylenedioxy-*N*-methylcathinone (also known as methylone, MDMC, bk-MDMA, or M1).⁶

NDIC uses the term *synthetic cathinone products* to refer to synthetic cathinones packaged as authentic commercial products. These products include purported beauty and household goods such as "bath salt" products sold as Bliss, Blizzard, Blue Silk, Charge+, Hurricane Charlie, Ivory Snow, Ivory Wave, Ocean Burst, Pure Ivory, Purple Wave, Red Dove, Snow Leopard, Star Dust, Vanilla Sky, White Dove, White Knight, White Rush, and White Lightning.⁷ Synthetic cathinone products are also marketed as plant food/fertilizer, insect repellent, pond cleaner, and vacuum fresheners.⁸

Synthetic cathinones are commonly distributed in powder, crystal, and liquid forms, but they are also available and abused in tablet and capsule forms.⁹ Some synthetic cathinone tablets and capsules have been marketed by distributors as ecstasy—forensic laboratories analyzing seized ecstasy tablets have reported that some tablets contain synthetic cathinones, alone or in combination with other drugs.¹⁰ However, these tablets and capsules have not been marketed in retail outlets or on the Internet in conjunction with the more widely recognized "bath salts."¹¹

Abusers typically ingest, inhale, inject, smoke, or snort (insufflate) synthetic cathinone products to experience effects similar to those of amphetamine abuse. Some abusers dissolve the drugs in water or other solvents and proceed to atomizeⁱ and inhale them, while others apply the solutions to their mucus membranes by placing drops in their eyes or spraying the solutions in their noses.¹²

The term *synthetic cathinone products*, as used in this report, is not meant to refer to legal pharmaceuticals. The prescription drugs bupropion (Zyban®, Wellbutrin®), diethylpropion (Tenuate®), and pyrovalerone (Centroton®) are legal synthetic cathinone products—diethylpropion is a Schedule IV controlled substance, and pyrovalerone is a Schedule V controlled substance under the Federal CSA.

i. Atomizers are devices that use heat, pressure, or vibration to convert a liquid into a vapor or an aerosol mist so it can be inhaled and absorbed through the lungs. Electronic cigarettes are a common type of atomizer that uses heat. Nebulizers—often used by individuals with respiratory disorders and diseases—use vibration or pressure.

Synthetic Cathinones (Bath Salts): An Emerging Domestic Threat

Synthetic Cathinone Availability and Abuse

NDIC assesses with high confidence that the availability of synthetic cathinone products in the United States is high.

State and local law enforcement information indicates that synthetic cathinone products are readily available in retail establishments and over the Internet, and some local independent dealers sell the products. Synthetic cathinone products, most marketed as “bath salts,” are distributed across the country in small, independently owned retail establishments such as adult stores, independently owned convenience stores, gas stations, head shops, and skateboard shops.¹³ The products, as well as their raw chemical components, are also sold on many Internet sites, including popular Internet auction sites and global marketing sites.¹⁴ The products are typically “branded” under the names previously listed. Some local independent drug dealers also distribute the products directly to users.¹⁵

Available seizure information indicates that significant quantities of synthetic cathinones and synthetic cathinone products are shipped to the United States from foreign countries. CBP seized many shipments of synthetic cathinones and synthetic cathinone products at U.S. POEs from July 2009 through April 2011; the products were laboratory tested and found to contain MDPV, mephedrone, and other synthetic cathinones that have not yet been identified in synthetic cathinone products distributed in the United States.¹⁶ Synthetic cathinone products are often packaged in such a way that they appear to be authentic beauty and household goods.¹⁷ As such, they pose a particular challenge for law enforcement officials in detection and interdiction efforts.

Cathinones are sometimes sold in combination with other synthetic drugs or marketed as different drugs altogether.

- In January 2011, the Centralia (MO) Police Department arrested three men in a school parking lot after they attempted to sell “Bliss,” a synthetic cathinone product mixed with methamphetamine, to an undercover officer. The 1/8-ounce powdered mixture was priced at \$200.¹⁸
- In September 2010, the San Luis Obispo (CA) Sheriff’s Department reported that two 15-year-old boys who thought they were consuming MDMA fell violently ill and developed small holes in their lungs after consuming mephedrone. The two boys also experienced symptoms of sore throat, violent vomiting, euphoria, elevated body temperature, and agitation. A nearby university student was arrested and charged with child endangerment and selling a narcotic substance to the teens.¹⁹ Later that same month, the university student’s mother was arrested after an investigation revealed that she had accepted and signed for a 2-pound package of mephedrone that had originated in China and had been delivered by the U.S. Postal Service.²⁰

Synthetic cathinone abuse has caused users throughout the country to experience severe adverse effects, and the number of “bath salt” calls to U.S. poison control centers has trended upward. On December 21, 2010, the American Association of Poison Control Centers (AAPCC) issued its first warning regarding the dangers of synthetic cathinone abuse, particularly for products marketed as “bath salts.” The warning informed the public that as of that date, at least 156^d

d. While the warning indicated at least 156 calls had occurred as of December 21, 2010, the AAPCC reported on May 12, 2011, that 302 “bath salt” calls were ultimately recorded for 2010.

“bath salt”-related calls had occurred in 2010—85 from Louisiana alone. Effects reported to the centers included increased blood pressure, increased heart rate, agitation, hallucinations, extreme paranoia, and delusions; no deaths were reported.²¹ The Louisiana Department of Health and Hospitals also issued a warning regarding synthetic cathinones (bath salts), mentioning several symptoms experienced by hospitalized patients in addition to those mentioned above, including chest pain, headache, and suicidal thoughts.²² From January 1 through May 12, 2011, the AAPCC received 2,237 “bath salt”-related calls from poison control centers in 47 states and the District of Columbia—a significant increase from the 302 calls recorded for all of 2010.²³ (See Table 1.)

Table 1. “Bath-Salt”-Related Calls Reported to U.S. Poison Control Centers

Year	Number of Calls
2009	0
2010	302
2011*	2,237

Source: American Association of Poison Control Centers, data run by AAPCC on May 12, 2011.

*Data reflect calls received and reported from January 1, 2011, through May 12, 2011.

Synthetic cathinones are used by a geographically and demographically diverse abuser population. No current U.S. population, household, or user survey contains questions regarding synthetic cathinones or synthetic cathinone products, but some indicators suggest the demand for and use of synthetic cathinone products are widespread. The AAPCC has issued multiple “bath salt abuse” press releases since December 2010, state health departments are posting “bath salt” warnings on their web sites,²⁴ and state^{e, 25} and local^f governments are introducing legislation and ordinances to reduce the availability of synthetic cathinones in their areas.²⁶ In addition, DEA National Forensic Information System (NFLIS) is receiving increasing reports of synthetic cathinone seizures. In 2009, NFLIS received 14 reports of analyzed seizures related to synthetic cathinones from 8 states; however, in 2010, NFLIS received 290 reports of analyzed seizures from 21 states.²⁷ The AAPCC reports that “bath salts” abuse patients seeking medical attention range from teenagers to those in their 40s.²⁸ Moreover, synthetic cathinone abusers likely are individuals who seek stimulant effects similar to those produced by cocaine, amphetamine/methamphetamine (illicit and prescription), and MDMA.²⁹

Synthetic cathinones abusers likely are attracted to the drugs because they can evade most drug testing. Most current routine drug testing screens do not detect the presence of synthetic cathinones. Consequently, the drugs may appeal to some abusers who are subject to mandatory drug testing. While synthetic cathinones are not detected by routine screens,^{g, 30} some commercial drug testing laboratories are beginning to offer specialized synthetic cathinone

e. As of May 4, 2011, according to the National Conference of State Legislatures, a total of 15 states had taken action to ban at least one of the chemicals used in drugs labeled as “bath salts,” either through legislative or administrative action; and 31 state legislatures have introduced legislation to restrict these substances.

f. Contact your county government for local “bath salt” ordinances.

g. Most drug testing companies offer an expanded test that includes a few additional drugs in the testing process. Typically the tests will look for a few of the following: ethanol (alcohol), hydrocodone (Lortab, Vicodin), barbiturates, methaqualone (Quaaludes), methadone, benzodiazepines (e.g., Valium), MDMA (ecstasy), propoxyphene (Darvon).

Synthetic Cathinones (Bath Salts): An Emerging Domestic Threat

testing.³¹ One commercial toxicology laboratory offers two “designer stimulant drug test” panels—one for MDPV and mephedrone and one for an expanded panel of 14 synthetic stimulants.³²

Synthetic cathinone abusers who operate motor vehicles while under the influence will likely go undetected during traffic stops unless toxicology testing for the drugs is specifically requested. Many synthetic cathinones produce stimulant effects that appear to be similar to cocaine, amphetamines/methamphetamine, and MDMA. As such, abusers who operate motor vehicles after using synthetic cathinones likely present similar dangers as those who operate motor vehicles while under the influence of controlled stimulants. However, the presence of synthetic cathinones in the systems of these “drugged drivers” likely will go undetected if they are stopped for a traffic offense unless the officer making the stop is aware of the signs of stimulant abuse and orders a specialized synthetic cathinone laboratory test.

Synthetic Cathinone Production and Distribution

Synthetic cathinone products are manufactured internationally. According to very limited domestic and European law enforcement reporting, synthetic cathinones are synthesized primarily in foreign countries, including China, India, and Pakistan. Cathinones are generally synthesized by rogue chemists in foreign countries and are shipped directly to distributors or acquired by distributors and abusers over the Internet. The United Kingdom has been identified as a principal transit country of some synthetic cathinones destined for the United States.³³ Synthetic cathinones are also marketed and sold on international and domestic web sites.³⁴

Synthetic cathinones are deliberately labeled and marketed to circumvent sales restrictions and evade prosecution. Manufacturers and distributors often advertise synthetic cathinone products as bath salts or plant food that are “not for human consumption” to evade FDA scrutiny.³⁵ However, if synthetic cathinone products are marketed or sold with the inference that they are “legal cocaine, methamphetamine, MDMA, LSD, etc.,” they can be regulated by the FDA as *street drug alternatives*.³⁶ The FDA considers any product that is promoted as a street drug alternative to be an unapproved new drug and a misbranded drug in violation of the Federal Food, Drug, and Cosmetic Act.³⁷ In addition, synthetic cathinones are not scheduled under the Federal CSA; however, possession and distribution of the synthetic cathinones may be prosecuted, albeit with greater difficulty, under the CSA’s Analogue Enforcement Act of 1986 (as amended), which states that the controlled substance analogues shall, “to the extent intended for human consumption,” be treated as Schedule I controlled substances.

Synthetic Cathinone Legislation and Regulations

State and local governments are adopting legislation and local ordinances to reduce the availability of synthetic cathinones in their jurisdictions, and members of the United States Congress have introduced legislation to nationally ban the sale of certain synthetic cathinones^h. As of May 2011, all 50 states and the District of Columbia had introduced legislation to restrict or ban some synthetic cathinones and cathinone derivatives.³⁸ Some legislation places specific cathinones on state lists of controlled substances.³⁹ Additionally, some local governments are banning synthetic cathinones or synthetic cathinone products ahead of state legislatures. As state legislation and local ordinances are enacted, abusers will likely travel to neighboring areas

h. S. 409, the “Combating Dangerous Synthetic Stimulants Act of 2011.”

without such legislation or ordinances to purchase synthetic cathinone products or acquire them via the Internet.

The DEA is gathering information on the pharmacology, toxicity, and abuse of synthetic cathinones and synthetic cathinone products to support possible scheduling under the Federal CSA. On March 31, 2011, the Drug and Chemical Evaluation Section (ODE) of the DEA Office of Diversion Control issued a public request for information on the following synthetic cathinones:

- **MDPV** *synonym* 3,4-methylenedioxyprovalerone
- **Mephedrone** *synonyms* 4-methylmethcathinone, 4-MMC
- **Methylone** *synonyms* 3,4-methylenedioxymethcathinone, MDMC
- **Naphyrone** *synonyms* naphthylpyrovalerone, NRG-1
- **4-Fluoromethcathinone** *synonyms* 4-FMC, flephedrone
- **3-Fluoromethcathinone** *synonym* 3-FMC
- **Methedrone** *synonyms* 4-methoxymethcathinone, BK-PMMA, PMMC
- **Butylone** *synonyms* bk-MBDB, beta-keto-N-methylbenzodioxolylpropylamine

Any information collected pursuant to ODE's request, particularly that related to law enforcement encounters, drug identification, toxicology reports, medical examiner reports, and abuse will be used to support appropriate administrative modification to the drug schedules—or proposed statutory revisions to the CSA—to include synthetic cathinones, if warranted.

Use of synthetic cathinones by members of the U.S. Armed Forces is prohibited. U.S. Armed Forces' offices have distributed general orders⁴⁰ prohibiting the use of intoxicating substances—substances that are inhaled, injected, consumed, or otherwise introduced into the body for the purpose of becoming intoxicated, high, altering mood or function, or achieving a psychoactive effect. Abuse of synthetic cathinones violates this order. Failure to obey this general order is a violation of Article 92, Uniform Code of Military Justice (UCMJ), and may result in disciplinary or administrative action including, but not limited to, trial by military court-martial, nonjudicial punishments under Article 15 of the UCMJ, reprimand, admonishment, administrative demotion, security clearance revocation, and involuntary separation with an adverse characterization of service.

Outlook

NDIC assesses with high confidence that the distribution and abuse of synthetic cathinones in the United States will increase in the near term. As of the date of this report, synthetic cathinone-related calls to U.S. poison control centers continue to increase. Despite previously described legislation and orders, no substantial law enforcement or regulatory action has significantly prevented synthetic cathinone products from reaching distributors or consumers, partly due to availability of the chemicals, drugs, and products on the Internet. Until effective policies become widespread and applied consistently and enforcement and regulatory actions begin to effect the supply-demand balance, demand for the products will continue to fuel their production and distribution.

Synthetic Cathinones (Bath Salts): An Emerging Domestic Threat

NDIC assesses with high confidence that more synthetic cathinones will be abused in the long term. Dozens of different synthetic cathinones have been developed, but only 12 have been seized and publicly identified.⁴¹ Other synthetic cathinones are likely to be exploited in reformulated products or as new products. The vast profit margin associated with these products and the ability of manufacturers and traffickers to sidestep international chemical regulations will inevitably increase the availability of these drugs and their marketing to susceptible abusers.

As commercial drug testing companies develop drug screens to detect synthetic cathinone abuse, different synthetic cathinones will surface. Commercial drug testing companies are developing drug screens to detect certain synthetic cathinones. However, because many distinct synthetic cathinones exist and their metabolism in the human body is not fully understood, the timely development of these tests will be difficult and the accuracy of initially developed tests will be limited. As tests are developed to screen for and detect the presence of the currently identified synthetic cathinones, manufacturers will synthesize additional synthetic cathinones, as manufacturers have done with other synthetic drugs. For instance, in response to testing and enforcement efforts, manufacturers of synthetic cannabinoids introduced lesser-known JWH-019 after widely used JWH-018 was able to be detected by tests and law enforcement placed pressure on manufacturers and distributors.⁴² (JWH-018 and JWH-019 are synthetic cannabinoids.)

The global nature of Internet chemical sales, particularly of synthetic cathinones, will present increasing challenges to U.S. law enforcement in the long term. If distribution of specific synthetic cathinones is successfully controlled in the United States through appropriate administrative control actions and legislation, producers will market other, unregulated synthetic cathinones and chemicals, particularly through the Internet and global shipping networks. Long-term control of synthetic cathinones will require significant international cooperation and coordinated enforcement efforts.

Appendix A. Common Synthetic Cathinones

Mephedrone (commonly known as 4-MMC, Bubbles, Drone, M-Cat, Meow Meow, and Meph) typically has little or no odor.⁴³ It is commonly available as a fine, white, off-white, or yellowish powder; in crystal form; as a tablet; or in capsules.⁴⁴ Mephedrone is sold in retail (1, 5, or 10 grams) and/or in bulk quantities. Effects are usually experienced 15–45 minutes after ingested and last approximately 2–5 hours. After snorting, effects are usually experienced in 30 minutes and last approximately 2–3 hours. After an intravenous injection, the effects last approximately 10–30 minutes.⁴⁵

MDPV is a drug variant of pyrovalerone and was first detected in Germany in 2007.⁴⁶ It is commonly available as a gray-colored substance with a granular consistency (the chemical form of its free base), a white powder (hydrochloride salt form), or as a tablet. Effects usually occur 15–30 minutes after ingestion and last approximately 2–7 hours. After snorting, effects are usually experienced in 5–20 minutes and last approximately 2–3.5 hours. Abuse of pyrovalerone has been reported in drug addicts,⁴⁷ so MDPV addiction may be possible.

Synthetic Cathinones (Bath Salts): An Emerging Domestic Threat

Appendix B. Scope and Methodology

Scope: This situation report examines the threat that synthetic cathinone abuse poses to the United States and the difficulty that U.S. law enforcement faces in preventing the manufacture and distribution of synthetic cathinones and synthetic cathinone products. This report does not examine the threat posed by prescription drugs that contain cathinones.

Source Summary Statement: The analysis in this situation report is primarily derived from data posted publicly by official U.S. and European Union Government agencies and international organizations, as well as studies published in peer-reviewed journals. The NDIC regards these sources as highly reliable and authoritative.

The cutoff date for all source reporting used in this assessment is May 18, 2011.

High Confidence generally indicates that judgments are based on high-quality information from multiple sources, from a single highly reliable source, or that the nature of the issue makes it possible to render a solid judgment. **Medium Confidence** generally means that the information is credibly sourced and plausible, but can be interpreted in various ways or is not of sufficient quality or corroborated sufficiently to warrant a higher level of confidence. **Low confidence** generally means that the information's credibility or plausibility is questionable, the information is too fragmented or poorly corroborated to make solid analytic inferences, or that NDIC has significant concerns or problems with the sources.



Re: Question on bath salts - MDPV 

Jocelyn Kula to: Christine Zaczynski

Cc: Denis Arsenault, Isabel Shanahan

2011-09-29 03:18 PM

Hi Christine,

~~You can still direct these questions to me. Hope this finds you well.~~

Re "bath salts" and MDPV, we have media lines on these although I am not convinced that I have the most recent version of them on hand; perhaps if you are getting a lot of questions, you could ask your comms person to get them from Christine Roush in the CSTD comms team in PACCB.

In short, these "bath salts" products appear to contain mephedrone and/or MDPV and they are definitely not approved drugs or even legitimate consumer goods like real bath salts are. Mephedrone is a controlled substance because it is an analog of amphetamine but MDPV is not currently included in the Schedules to the CDSA.

Let me know if you need anything else.

Jocelyn

Isabel- pls print for our Mephedrone file

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire

Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada/ Santé Canada

Tel: (613) 946-0125 Fax: (613) 946-4224

Christine Zaczynski Hi Jocelyn, Hope all is well with you. I'm not s... 2011-09-29 07:46:43 AM

From: Christine Zaczynski/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2011-09-29 07:46 AM
Subject: Question on bath salts - MDPV

Hi Jocelyn,

Hope all is well with you. I'm not sure if you are still the right person to contact about these types of questions - if not please let me know!

We just had a question about the status "bath salts", or MDPV. Is this a substance under review by your office? We do not have any incidents at this time but it was a general question as it was just in the media:

<http://telegraphjournal.canadaeast.com/city/article/1442171>

Thanks!

Christine



**CONGRESSIONAL BUDGET OFFICE
COST ESTIMATE**

October 18, 2011

**S. 409
Combating Dangerous Synthetic Stimulants Act of 2011**

As reported by the Senate Committee on the Judiciary on July 28, 2011

CBO estimates that implementing S. 409 would have no significant costs to the federal government. Enacting the bill could affect direct spending and revenues; therefore, pay-as-you-go procedures apply. However, CBO estimates that any effects would be insignificant for each year.

S. 409 would permanently expand the list of substances regulated by the Drug Enforcement Administration (DEA) to include two new synthetic drugs commonly known as bath salts. As a result, the government might be able to pursue cases involving drug use that it otherwise would not be able to prosecute. CBO expects that S. 409 would apply to a relatively small number of additional offenders, however, so any increase in costs for law enforcement, court proceedings, or prison operations would not be significant. Any such costs would be subject to the availability of appropriated funds.

Because those prosecuted and convicted under S. 409 could be subject to criminal fines, the federal government might collect additional fines if the legislation is enacted. Criminal fines are recorded as revenues, deposited in the Crime Victims Fund, and later spent. CBO expects that any additional revenues and direct spending would not be significant because of the small number of cases likely to be affected.

S. 409 contains no intergovernmental mandates as defined in the Unfunded Mandates Reform Act (UMRA) and would impose no costs on state, local or tribal governments.

Under current law, DEA plans to control the two synthetic stimulants listed in the bill by adding them to schedule I temporarily under the agency's emergency scheduling authority. The temporary restrictions under schedule I could go into effect as early as mid-October 2011 and would expire one year later (with the possibility of a six-month extension). During this period, the Department of Health and Human Services (HHS) would conduct a formal rulemaking process to determine if the chemicals should be permanently controlled under schedule I.

If HHS does not make a determination to permanently control the chemicals, the bill would do so and would impose private-sector mandates as defined in UMRA. CBO estimates that

the cost of complying with the mandates, if imposed, would probably exceed the annual threshold established in UMRA for private-sector mandates (\$142 million in 2011, adjusted annually for inflation).

By adding the two synthetic stimulants to schedule I of the Controlled Substances Act, the bill would prohibit the manufacture, sale, or distribution of those chemicals. The cost of the prohibition would be the forgone profits from lost sales, including the wholesale cost of the inventory of the newly banned products held by sellers after enactment. Because of the nature of the market being regulated, the scope of sales affected is difficult to determine. Some industry experts estimate that the profits generated by the sale of products containing such synthetic chemicals amount to billions of dollars annually.

Industry data and information provided by law enforcement officials suggests that the markets for synthetic stimulants have adjusted very quickly in the past to replace chemicals or redirect sales in response to state-level bans on MDPV and Mephedrone and the chemicals remain widely available. However, given the estimated magnitude of industry profits, even a 5 percent decrease in industry profits as a result of the ban would probably exceed the annual threshold for private-sector mandates. Most of those costs would be incurred within the first two years the mandate is in effect.

The bill also would impose a mandate by prohibiting the unregistered possession of the two banned stimulants, requiring individuals and facilities that wish to use or handle the chemicals to register with the DEA. Individuals who cannot obtain DEA approval would be required to dispose of the banned chemicals in their possession. According to the DEA, once registrants have been approved to use or handle schedule I chemicals, they do not need to register again when the schedule is updated. Also, most individuals and facilities that would need to handle the chemicals listed in the bill have already registered. Therefore, CBO expects that the cost of this mandate to the private sector would be small.

The CBO staff contacts for this estimate are Mark Grabowicz (for federal costs) and Marin Randall (for the impact on the private sector). The estimate was approved by Theresa Gullo, Deputy Assistant Director for Budget Analysis.

News Release
FOR IMMEDIATE RELEASE
October 21, 2011
Contact: DEA Public Affairs
Number: 202-307-7977

10/21/11
→ Oct. 21, 2011

Chemicals Used in "Bath Salts" Now Under Federal Control and Regulation

DEA Will Study Whether To Permanently Control Three Substances

OCT 21 - WASHINGTON, D.C. – The United States Drug Enforcement Administration (DEA) today exercised its emergency scheduling authority to control three synthetic stimulants (Mephedrone, 3,4 methylenedioxypropylamphetamine (MDPV) and Methylone) used to make products marketed as "bath salts" and "plant food". Except as authorized by law, this action makes possessing and selling these chemicals, or the products that contain them, illegal in the United States. This emergency action was necessary to prevent an imminent threat to the public safety. The temporary scheduling action will remain in effect for at least one year while the DEA and the United States Department of Health and Human Services (DHHS) further study whether these chemicals should be permanently controlled.

The Final Order was published today in the Federal Register to alert the public to this action. These chemicals will be controlled for at least 12 months, with the possibility of a six month extension. They are designated as Schedule I substances, the most restrictive category under the Controlled Substances Act. Schedule I status is reserved for those substances with a high potential for abuse, no currently accepted use for treatment in the United States and a lack of accepted safety for use of the drug under medical supervision.

Over the past several months, there has been a growing use of, and interest in, synthetic stimulants sold under the guise of "bath salts" or "plant food". Marketed under names such as "Ivory Wave", "Purple Wave", "Vanilla Sky" or "Bliss", these products are comprised of a class of chemicals perceived as mimics of cocaine, LSD, MDMA, and/or methamphetamine. Users have reported impaired perception, reduced motor control, disorientation, extreme paranoia, and violent episodes. The long-term physical and psychological effects of use are unknown but potentially severe. These products have become increasingly popular, particularly among teens and young adults, and are sold at a variety of retail outlets, in head shops and over the Internet. However, they have not been approved by the FDA for human consumption or for medical use, and there is no oversight of the manufacturing process.

In the last six months, DEA has received an increasing number of reports from poison control centers, hospitals and law enforcement regarding products containing one or more of these chemicals. Thirty-seven states have already taken action to control or ban these or other synthetic stimulants. The Comprehensive Crime Control Act of 1984 amends the Controlled Substances Act (CSA) to allow the DEA Administrator to temporarily schedule an abused, harmful, non-medical substance in order to avoid an imminent hazard to public safety while the formal rule-making procedures described in the CSA are being conducted.

"This action demonstrates our commitment to keeping our streets safe from these and other new and emerging drugs that have decimated families, ruined lives, and caused havoc in communities across the country," said DEA Administrator Michele M. Leonhart. "These chemicals pose a direct and significant threat, regardless of how they are marketed, and we will aggressively pursue those who attempt their manufacture and sale."

27



Re: U.S. / Bath Salts Article in Today's News Summary

Jocelyn Kula to: Tara E Phillips

2011-10-24 10:03 AM

Angela Doyle, Denis Arsenault, Elizabeth Dussault, Hong Zhang,
Cc: Jonas Langille, Justine Radulovic, Martina Vorel, Nathan J Isotalo,
Salha Jumbe, Stephanie Chandler

	Tara E Phillips	U.S. / Bath Salts Article in Today's News Summary
	Jocelyn Kula	<i>Thanks Tara, We have a file on Mephedrone and Salha can add this.</i>

Thanks Tara,

We have a file on Mephedrone and Salha can add this.

Jocelyn

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224

Tara E Phillips

2011-10-24 09:58:23 AM

From: Tara E Phillips/HC-SC/GC/CA
To: Angela Doyle/HC-SC/GC/CA@HWC, Denis Arsenault/HC-SC/GC/CA@HWC, Stephanie
Chandler/HC-SC/GC/CA@HWC, Elizabeth Dussault/HC-SC/GC/CA@HWC, Nathan J
Isotalo/HC-SC/GC/CA@HWC, Salha Jumbe/HC-SC/GC/CA@HWC, Jocelyn
Kula/HC-SC/GC/CA@HWC, Jonas Langille/HC-SC/GC/CA@HWC, Justine
Radulovic/HC-SC/GC/CA@HWC, Martina Vorel/HC-SC/GC/CA@HWC, Hong
Zhang/HC-SC/GC/CA@HWC
Date: 2011-10-24 09:58 AM
Subject: U.S. / Bath Salts Article in Today's News Summary

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PUBLICATION: The Kingston
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DATE: 2011.10.22

EDITION: Final

SECTION: News

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U.S. bans chemicals in 'bath salts' street drug

WASHINGTON -- U.S. authorities Friday issued a temporary ban on chemicals used in a new type of street drug known as "bath salts" that is increasingly popular among teens.

The Drug Enforcement Administration (DEA) took emergency action that makes possessing and selling these chemicals or products that contain them illegal in the United States. "This emergency action was necessary to prevent an imminent threat to public **safety**," the DEA said in a statement.

Under the federal order, the **chemicals** used to make bath salts -- mephedrone, methylenedioxypropylvalerone (MDPV) and methylone -- are banned for at least one year.

Studies will then determine if the chemicals should be permanently banned.

The action places the chemicals on the DEA's most restrictive list, reserved for substances with high potential for abuse and that do not have a currently accepted use for treatment.

Bath salts are marketed with catchy names like "Ivory Wave," "Purple Wave," "Vanilla Sky," and "Bliss," and are comprised of chemicals that mimic the effects of drugs like cocaine and LSD, authorities said.

Users have reported impaired perception, reduced motor control, disorientation, extreme paranoia and violent episodes, with other unknown longer-term physical and psychological effects.

Bath salts, also sometimes sold as "plant food," are growing in popularity among young adults and teens. They are sold at tobacco shops, gas stations, convenience stores and online, according to the DEA.

The products are typically marked "not for human consumption" but are commonly snorted, swallowed or injected by users. They have not been approved by the federal regulators for human consumption or medical use.

Poison control centers, hospitals and police have been fielding an increasing number of calls about products containing the **chemicals** in bath salts, the DEA said.

[Back](#)

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Bangor police officer details scourge of 'bath salts' designer drug

SAINT JOHN - When Bangor police get a call about a shirtless, agitated and aggressive man on the streets, it's likely to be someone high on bath salts, a new designer drug that's taken the Maine city by storm.

"We never expected this tidal wave, this tsunami of drugs that came in and stayed," said Lieut. Thomas Reagan, a drug recognition expert with the Bangor Police Department.

Reagan, who was making a public presentation at Ridgewood Addiction Services on Thursday night, says his department gets more than 80 calls a day about people who are dangerously hallucinating or delirious on the highly addictive drug.

Bath salts is a nickname, and the drug has nothing to do with bath **products**. Other nicknames include plant food and research **chemicals**. In Bangor, it's known as monkey dust.

On one recent occasion, police responded to a man standing shirtless in the night, who was cutting his arms, trying to get out bugs he believed were crawling under his skin.

Another time, police were called to a home where a man high on bath salts had locked himself in the bathroom. He believed voices were saying they would kill him. He smashed his sink and toilet, sticking pieces under the door when he thought he saw the barrel of a gun slide beneath the door.

Hallucinations are so real for people high on bath salts, they will go to drastic and often violent measures to protect themselves, Reagan said.

"You don't know what you're going to get," he said. "They're unpredictable."

Arrested addicts are often found with knives, guns and brass knuckles that are mostly used as protection against demons of their own imaginations.

But though Bangor is a little more than three hours away, Saint John police have no evidence the synthetic drug - which is widely available online - has reached the Port City.

"There are no confirmed cases of it and that's important," said Sgt. David Hartley-Brown, of the Saint John Police Force. The Rothesay Regional Police Force and Ridgewood Addiction Services also hosted the talk, which occurred during National Addictions Awareness Week.

Bath salts causes euphoria, similar to methamphetamine, Reagan said. But it can be made from any number of chemicals, including MDPV, mephedrone or methylene.

"There's no quality control on this stuff," he said.

The powder is most often smoked like crack cocaine, as well as snorted or injected.

The drug first started popping up in Bangor in December 2010 and has gone from crisis to epidemic levels, Reagan said.

It caught law enforcements off-guard - not only because of the dangerous nature of the high, but because the substance wasn't actually illegal in the United States until last month.

He warned that Saint John and New Brunswick should push to make the substance illegal here before it's too late.

"You've got to get some strong laws that give you teeth," he said. In Maine, possession of bath salts can land you in jail for a year. Aggressive trafficking - such as selling to children or using a weapon - can net a 25-year sentence.

Reagan said the drug is popular among people who are already junkies, and often, those who abuse prescription drugs. So far it has not hit the Bangor high schools.

Bath salts is also cheap, at \$15 for a tenth of a gram, which would be enough for the night, he said. The drug is abundant, until recently it was legal, and it usually doesn't show in a urine test.

"We had a lot of addicts legally on this stuff before the law came into effect," he said. "Now we have to back track."

Most emergency calls land bath salt users in hospitals because they have dangerously high heart rates and body temperatures. The users are also more likely to commit suicide.

Increased use of firearms is also a concern, he said.

Reagan said he was planning to hang around Saint John on Friday to see if he could track down any bath salts in local head shops or on the street.

The lieutenant will speak again at Kennebecasis Valley High School on Friday at 2 p.m.

29



Fw: Bath Salt info

Denis Arsenault to: Salha Jumbe

2011-11-18 08:42 AM

Denis Arsenault	Fw: Bath Salt info
-----------------	--------------------

Hi Salha,

Please ensure these documents are in the mephedrone/bath salts file.

Denis

Denis Arsenault,
Section Head - Policy / Chef - Section des politiques
Regulatory Policy Division /
Division des politiques réglementaires,
Office of Controlled Substances /
Bureau des substances contrôlées,
Health Canada / Santé Canada
Tel/Tél: (613) 957-6828
Fax / Télécopieur : (613) 946-4224
E-Mail/Courriel: denis.arsenault@hc-sc.gc.ca

----- Forwarded by Denis Arsenault/HC-SC/GC/CA on 2011-11-18 08:41 AM -----

From: Jocelyn Kula/HC-SC/GC/CA
To: Denis Arsenault/HC-SC/GC/CA@HWC
Date: 2011-11-06 09:58 PM
Subject: Fw: Bath Salt info

more bath salt info for our MDPV/ mephedrone file pls

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224
----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2011-11-06 09:57 PM -----

From: Benoit Archambault/HC-SC/GC/CA
To: Guy Aucoin/HC-SC/GC/CA@HWC, Johanne Beaulieu/HC-SC/GC/CA@HWC, Jocelyn Kula/HC-SC/GC/CA@HWC, Evelyn Soo/HC-SC/GC/CA@HWC, Julie Bernier/HC-SC/GC/CA@HWC, Andre Fouquet/HC-SC/GC/CA@HWC
Date: 2011-10-03 03:20 PM

Subject: Bath Salt info

FYI

Benoit Archambault
Gestionnaire Laboratoire/Lab Manager
Service Analyse des Drogues/Drug Analysis Service
Santé Canada/Health Canada

Tel : 450.928.4027

Fax: 450.928.4144

Cel.: 514.973.0823

benoit.archambault@hc-sc.gc.ca

----- Transféré par Benoit Archambault/HC-SC/GC/CA le 2011-10-03 15:19 -----

s.19(1)

From: [REDACTED]

Sent: Thursday, September 29, 2011 11:26 AM

To: [REDACTED]

Cc: Real Vallee (real.vallee@rcmp-grc.gc.ca); Lori Mitchell (lori.mitchell@cbsa-asfc.gc.ca); Marie-Claude Cellard (marie-claude.cellard@rcmp-grc.gc.ca); Jean-Francois Robert (jean-francois.robert@rcmp-grc.gc.ca); Sylvain Hamel (sylvain.hamel@rcmp-grc.gc.ca); [REDACTED]; [REDACTED]; [REDACTED]

Subject: Bath Salt info

Information regarding the "Bath Salt" epidemic; Bangor, ME is currently the hot spot, but I've heard reports that it has spread to central NH.

Attached are FPS Informational Bulletin, current Maine Law regarding "bath salts", and fact sheet by the Office of Substance Abuse.

For informational purposes only, please disseminate to other Law Enforcement that may encounter this substance.

I will forward the Maine FUSION Center/Bangor PD powerpoint as soon as it becomes available.

[REDACTED]
Inspector, FPS/DHS

40 Western Ave, Room 209A, Augusta, ME 04330

Office (207) 622-8230

Cell (617) 828-2550

Fax (207) 622-8231



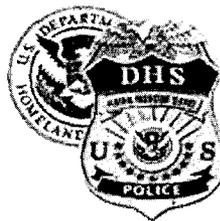
01-IB-068-2011.pdf



HP114706.pdf



OSA _ Fact Sheet.pdf



HP1147, LD 1562, item 6, 125th Maine State Legislature , Amendment
H "A" to C "A", Filing Number H-676, Sponsored by WEBSTER

PLEASE NOTE: Legislative Information *cannot* perform research, provide legal advice, or interpret Maine law. For legal assistance, please contact a qualified attorney.

Amend the amendment by striking out everything after the enacting clause and before the emergency clause and inserting the following:

‘Sec. 1. 22 MRSA §§2390 to 2394 are enacted to read:

§ 2390. Unlawful possession of certain synthetic hallucinogenic drugs

1. Unlawful possession. It is unlawful for a person to possess certain synthetic hallucinogenic drugs if the person intentionally or knowingly possesses what that person knows or believes to be a certain synthetic hallucinogenic drug, which is in fact a certain synthetic hallucinogenic drug, and the drug is:

- A. 3, 4 - methylenedioxymethcathinone, MDMC;
- B. 3, 4 - methylenedioxypropylvalerone, MDPV;
- C. 4 - methylmethcathinone, 4-MMC;
- D. 4 - methoxymethcathinone, bk-PMMA, PMMC;
- E. 3 - fluoromethcathinone, FMC;
- F. 4 - fluoromethcathinone, FMC;
- G. Naphthylpropylvalerone, NRG-1; and
- H. Beta-keto-N-methylbenzodioxolylpropylamine.

2. Penalties. The following penalties apply.

- A. A person who violates this section commits a civil violation for which a fine of not more than \$350 may be adjudged.
- B. A person who violates this section after having been previously adjudicated of violating this section commits a civil violation for which a fine of not more than \$500 may be adjudged.
- C. A person who violates this section after having been previously adjudicated of violating this section 2 or more times commits a Class E crime.

3. Repeal. This section is repealed June 15, 2013.

§ 2391. Unlawful trafficking in certain synthetic hallucinogenic drugs

HP1147, LD 1562, item 6, 125th Maine State Legislature , Amendment
H "A" to C "A", Filing Number H-676, Sponsored by WEBSTER

1. Unlawful trafficking. It is unlawful for a person to traffick in certain synthetic hallucinogenic drugs if the person intentionally or knowingly trafficks in what the person knows or believes to be a certain synthetic hallucinogenic drug, which is in fact a certain synthetic hallucinogenic drug listed in section 2390. For purposes of this section, "traffick" has the same meaning as in Title 17#A, section 1101, subsection 17.

2. Penalties. The following penalties apply.

A. A person who violates this section commits a Class E crime.

B. A person who violates this section after having been previously adjudicated of violating this section commits a Class D crime.

3. Use of a motor vehicle. If a person uses a motor vehicle to facilitate the trafficking in a certain synthetic hallucinogenic drug listed in section 2390, the court may, in addition to other authorized penalties, suspend the person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license for a period not to exceed 5 years. A suspension may not begin until after any period of incarceration is served. If the court suspends a person's driver's license or permit, privilege to operate a motor vehicle or right to apply for or obtain a license, the court shall notify the Secretary of State of the suspension and the court shall take physical custody of the person's license or permit. The Secretary of State may not reinstate the person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license unless the person demonstrates that, after having been released and discharged from any period of incarceration that may have been ordered, the person has served the period of suspension ordered by the court.

4. Repeal. This section is repealed June 15, 2013.

§ 2392. Aggravated trafficking in certain synthetic hallucinogenic drugs

1. Unlawful aggravated trafficking. A person is guilty of aggravated trafficking in certain synthetic hallucinogenic drugs if the person violates section 2391 and:

A. The person trafficks in a certain synthetic hallucinogenic drug with a child who is in fact less than 18 years of age;

B. At the time of the offense, the person has one or more prior adjudications for any violation under this chapter or for engaging in substantially similar conduct in another jurisdiction;

C. At the time of the offense, the person possesses a firearm in the furtherance of the offense, uses a firearm, carries a firearm or is armed with a firearm;

D. At the time of the offense, the person is on a school bus or within 1,000 feet of the real property comprising a private or public elementary or secondary school or a safe zone as defined in Title 17#A, section 1101, subsection 23. For purposes of this paragraph, "school bus" has the same meaning as defined in Title 29#A, section 2301, subsection 5; or

HP1147, LD 1562, item 6, 125th Maine State Legislature, Amendment
H "A" to C "A", Filing Number H-676, Sponsored by WEBSTER

E. At the time of the offense, the person enlists or solicits the aid of or conspires with a child who is in fact less than 18 years of age to traffick in a certain synthetic hallucinogenic drug.

2. Penalty. Violation of this section is a Class C crime.

3. Use of a motor vehicle. If a person uses a motor vehicle to facilitate the aggravated trafficking in a certain synthetic hallucinogenic drug, the court may, in addition to other authorized penalties, suspend the person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license for a period not to exceed 5 years. A suspension may not begin until after any period of incarceration is served. If the court suspends a person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license, the court shall notify the Secretary of State of the suspension and the court shall take physical custody of the person's license or permit. The Secretary of State may not reinstate the person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license unless the person demonstrates that, after having been released and discharged from any period of incarceration that may have been ordered, the person has served the period of suspension ordered by the court.

4. Repeal. This section is repealed June 15, 2013.

§ 2393. Unlawfully furnishing certain synthetic hallucinogenic drugs

1. Unlawful furnishing. It is unlawful for a person to furnish certain synthetic hallucinogenic drugs if the person intentionally or knowingly furnishes what the person knows or believes to be a certain synthetic hallucinogenic drug, which is in fact a certain synthetic hallucinogenic drug listed in section 2390.

2. Penalties. The following penalties apply.

A. A person who violates this section commits a Class E crime.

B. A person who violates this section after having been previously adjudicated as violating this section commits a Class D crime.

3. Use of a motor vehicle. If a person uses a motor vehicle to facilitate the unlawful furnishing of a certain synthetic hallucinogenic drug, the court may, in addition to other authorized penalties, suspend the person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license for a period not to exceed 5 years. A suspension may not begin until after any period of incarceration is served. If the court suspends a person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license, the court shall notify the Secretary of State of the suspension and the court shall take physical custody of the person's license. The Secretary of State may not reinstate the person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license unless the person demonstrates that, after having been released and discharged from any period of incarceration that may have been ordered, the person has served the period of suspension ordered by the court.

4. Repeal. This section is repealed June 15, 2013.

HP1147, LD 1562, item 6, 125th Maine State Legislature , Amendment
H "A" to C "A", Filing Number H-676, Sponsored by WEBSTER

§ 2394. Aggravated furnishing of certain synthetic hallucinogenic drugs

1. Aggravated furnishing. A person is guilty of aggravated furnishing of certain synthetic hallucinogenic drugs if the person violates section 2393 and:

A. The person furnishes a certain synthetic hallucinogenic drug to a child who is in fact less than 18 years of age;

B. At the time of the offense, the person has one or more prior adjudications for any violation under this chapter or for engaging in substantially similar conduct in another jurisdiction;

C. At the time of the offense, the person possesses a firearm in the furtherance of the offense, uses a firearm, carries a firearm or is armed with a firearm;

D. At the time of the offense, the person is on a school bus or within 1,000 feet of the real property comprising a private or public elementary or secondary school or a safe zone as defined in Title 17#A, section 1101, subsection 23. For purposes of this paragraph, "school bus" has the same meaning as defined in Title 29#A, section 2301, subsection 5; or

E. At the time of the offense, the person enlists or solicits the aid of or conspires with a child who is in fact less than 18 years of age to furnish a certain synthetic hallucinogenic drug.

2. Penalty. Violation of this section is a Class D crime.

3. Use of a motor vehicle. If a person uses a motor vehicle to facilitate the aggravated furnishing of a certain synthetic hallucinogenic drug, the court may, in addition to other authorized penalties, suspend the person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license for a period not to exceed 5 years. A suspension may not begin until after any period of incarceration is served. If the court suspends a person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license, the court shall notify the Secretary of State of the suspension and the court shall take physical custody of the person's license or permit. The Secretary of State may not reinstate the person's driver's license or permit or privilege to operate a motor vehicle or right to apply for or obtain a license unless the person demonstrates that, after having been released and discharged from any period of incarceration that may have been ordered, the person has served the period of suspension ordered by the court.

4. Repeal. This section is repealed June 15, 2013.

Sec. 2. Maine Revised Statutes headnote amended; revision clause. In the Maine Revised Statutes, Title 22, chapter 558, in the chapter headnote, the words "marijuana, scheduled drugs, imitation scheduled drugs and hypodermic apparatuses" are amended to read "marijuana, scheduled drugs, imitation scheduled drugs, certain synthetic hallucinogenic drugs and hypodermic apparatuses" and the Revisor of Statutes shall implement this revision when updating, publishing or republishing the statutes.'

HP1147, LD 1562, item 6, 125th Maine State Legislature , Amendment
H "A" to C "A", Filing Number H-676, Sponsored by WEBSTER

SUMMARY

This amendment reallocates the restriction on the use, trafficking or possession of so-called bath salts proposed in Committee Amendment "A" from the Maine Criminal Code to the Maine Revised Statutes, Title 22 and changes some of the penalties to civil violations and reduces other criminal penalties.

BATH SALTS

June 2011

What are they?

Unregulated psychoactive substances marketed as "bath salts" are among the latest in a series of legal synthetic substances that, when used improperly, offer alternatives to illegal drugs. Suspected as being produced as legal substitutes for ecstasy, cocaine, and amphetamines, "bath salts" are powerful stimulant drugs that are suspected to have been designed to avoid legal prosecution, and are commonly available on the Internet and in specialty smoke shops.

Appearance:

"Bath salts" appear as pure white to light brown substances and are made up of a water dissolvable, crumbly powder with a slight odor. They are packaged as "soothing bath salts" and marketed under a variety of names such as Ivory Wave, Vanilla Sky, and White Rush. The packages are labeled "concentrated bath salts" and are usually sold in 200mg, 250mg, or 500mg packets. "Bath salt" products often contain a note declaring "not for human consumption". The list of ingredients on "bath salt" products often gives no indication of the presence of psychoactive substances. Although labeled as "soothing bath salts" to get around food and drug legislation, they sell for around \$30 per 500mg packet. These "bath salts" give users a euphoric feeling after they snort it, said to be "more intense than that brought on by cocaine."

Uses:

Although "bath salt" products contain no specific directions for use, they are usually snorted, but can also be smoked or swallowed.

Toxicity & Side Effects:

"Bath salt" products are known to produce certain side effects, some of which are quite severe. The following is the list of milder, short-term side effects associated with consumption of this drug as reported by available open sources:

- Increased heart rate
- Agitation
- Diminished requirement for sleep
- Lack of appetite
- Increased alertness and awareness
- Anxiety
- Fits and delusions
- Nosebleeds

More serious side effects associated with these drugs reportedly include:

- Blood circulation problems, including increased blood pressure
- Seizures
- Muscle spasms
- Muscle damage
- Loss of bowel control
- Hallucinations
- Aggression
- Severe paranoia
- Panic attacks
- Sharp increase in body temperature
- Risk of renal failure

Street Names:

The following is a sample of designer "bath salt" products associated with unregulated psychoactive substances that are potentially harmful:

- Ivory Wave
- Vanilla Sky
- Pure Ivory
- Whack
- Bolivian Bath
- Purple Wave
- Charge+
- Ocean Burst
- Sextacy
- Gloom
- Purple Rain
- Salt
- Fly
- Hurricane Charlie
- Crush
- White Rush

Legality:

Already, several states have introduced legislation to ban bath salts. Several counties, cities, and local municipalities have also taken action to ban these products. The Maine legislature is also in the process of enacting a ban on bath salts.

For more information or to find substance abuse treatment services contact:

**Maine Office of Substance Abuse
Information and Resource Center**

41 Anthony Ave.
11 State House Station
Augusta, ME 04333-0011

1-800-499-0027 or
(207)287-8900
Fax: (207) 287-8910
TTY: 1-800-606-0215
Email: osa.ircosa@maine.gov

Information compiled from:

- Florida Department of Law Enforcement "New Unregulated Psychoactive Substances Marketed as 'Bath Salts,'"
- Office of National Drug Control Policy's "Statement from White House Drug Policy Director on Synthetic Stimulants, a.k.a "Bath Salts,"
- Northern New England Poison Center "Bath Salts (Illegal, Fake)."



Office of Substance Abuse
An Office of the
Department of Health and Human Services

Paul R. LaPage, Governor

Mary C. Mayhew, Commissioner

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33



Fw: Bath salt document from last RCMP SDI meeting.

Denis Arsenault to: Salha Jumble

2011-11-18 08:51 AM

Denis Arsenault	Fw: Bath salt document from last RCMP SDI meeting.
-----------------	--

Hi Salha,

Again, please ensure these documents are in the mephedrone/bath salts file.

Denis

Denis Arsenault,
Section Head - Policy / Chef - Section des politiques
Regulatory Policy Division /
Division des politiques réglementaires,
Office of Controlled Substances /
Bureau des substances contrôlées,
Health Canada / Santé Canada
Tel/Tél: (613) 957-6828
Fax / Télécopieur : (613) 946-4224
E-Mail/Courriel: denis.arsenault@hc-sc.gc.ca

----- Forwarded by Denis Arsenault/HC-SC/GC/CA on 2011-11-18 08:43 AM -----

From: Jocelyn Kula/HC-SC/GC/CA
To: Denis Arsenault/HC-SC/GC/CA@HWC
Date: 2011-10-18 09:54 PM
Subject: Fw: Bath salt document from last RCMP SDI meeting.

and can you pls add to file on Mephedrone/ MDPV

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224
----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2011-10-18 09:54 PM -----

From: Mark Kozlowski/HC-SC/GC/CA
To: jocelyn.kula@hc-sc.gc.ca, johanne.beaulieu@hc-sc.gc.ca, carol.langlois@hc-sc.gc.ca
Date: 2011-10-18 12:42 PM
Subject: Bath salt document from last RCMP SDI meeting.

FYI

This document was provided at the last RCMP SDI meeting.



MK Scan001.PDF

**Fw: CBC.ca/health - Hallucinogenic 'bath salts' entering Canada**

Jocelyn Kula to: Salha Jumbe

2012-01-03 10:13 AM

Jocelyn Kula	Fw: CBC.ca/health - Hallucinogenic 'bath salts' entering Canada
--------------	---

can you pls print and add to our mephedrone file

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire

Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs

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From: HC_Media_SC/HC-SC/GC/CA

To:

Date: 2011-12-29 08:36 AM

Subject: CBC.ca/health - Hallucinogenic 'bath salts' entering Canada

Sent by: Hisham Kelati

Distribution group/Groupe de distribution: Controlled Substances - Substances contrôlées - HECSB/DGSESC, Pharmaceuticals Biologics and Genetic Therapies - HPFB/DGPSA,

CBC.ca/health

Hallucinogenic 'bath salts' entering Canada

<http://www.cbc.ca/news/health/story/2011/12/29/drug-bathsalts-1229.html>

The use of a synthetic hallucinogenic drug known as "bath salts" has begun to emerge in Canada, raising concern among health and law enforcement officials.

The powerful white powder is also known by the name mephedrone and is reported to cause anxiety, delusions and dangerously high blood pressure, as well as occasionally violent behaviour.

The drug is popular in England and the U.S. and now is starting to show up in Canada. It can be ordered legally and inexpensively over the internet in the United States.

Sgt. Paul Edwards of the Bangor, Maine, police told CBC News he would never forget when bath salts first showed up in the city. It was April, and he had just pulled over a driver he suspected was driving drunk.

"Basically, she had her rear end up on the ... back rest," he said. "Her body was so contorted and writhing she could not, could not stop."

Within weeks, he said, the drug had spread through the city: "We were dealing with this every single day, several times a day."

In Canada, Dr. Margaret Thompson, director of the Ontario Poison Centre, said bath salts are just starting to emerge. She first saw a patient on the drug last summer.

"We probably were seeing them and didn't know what they were, and our usual drug screens were coming back negative, but we still had a feeling the patient was high on something," she said.

The drug is illegal in Canada.

Thompson said there have been reports of people high on the substance in Toronto, central Ontario and Calgary.

She said all varieties of these bath salts are synthetic derivatives of the drug khat, a plant stimulant popular in parts of East African and the Mideast, but their composition can vary.

Violent behaviour

"You think you're getting something that's like khat, and it could be cut with all sorts of other stuff," she said. "It could be one per cent of the active ingredient, but it might be 100 per cent."

Thompson said the drug increases people's heart rate and blood pressure, and it sometimes causes hallucinations, violent behaviour, or seizures.

The drug is among several new synthetic designer drugs sold online or in small shops as actual bath salts or plant food.

They are packaged as "soothing bath salts" to get around U.S. federal laws and are also marketed as plant fertilizer. The drugs are marketed under names such as Cloud 9, Ivory Wave, Vanilla Sky and White Rush and are sold over the counter in states that haven't banned them.

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DRAFT – March 5, 2012

→ Drafted by
Angela
Doyle

Mephedrone and MDPV in Bath Salts

What are the ingredients found in bath salts?

Preliminary reports indicate that the psychoactive ingredients contained in “bath salts” products include mephedrone and/or MDPV.

Media coverage on this issue has been limited and does not point to widespread use of “bath salt” products in the general population.

From January 2010 up until now, Health Canada’s Drug Analysis Service (DAS) has tested 332 exhibits found to containing MDPV or mephedrone, 315 of these exhibits were found to contain MDPV alone; in fact, only 17 were found to contain mephedrone.

It must be emphasized, however, that DAS has no way of verifying whether these samples are from “bath salt” products or from other street drugs. When submitting exhibits for testing, law enforcement agencies are not required to provide DAS with any information as to the source or product a sample was taken from. As a result, DAS would never be able to attest to the fact that a given sample found to contain MDPV came specifically from a seizure of “bath salts”. It may be possible, however, for law enforcement agencies to make a linkage between a given seizure of “bath salt” products and positive results for MDPV found in analyses conducted by DAS.

In those cases where these products have been found to contain mephedrone, law enforcement agencies can take action as mephedrone is already considered to be a controlled substance under the *Controlled Drugs and Substances Act* (CDSA).

What is mephedrone?

Mephedrone is a synthetic amphetamine-type stimulant also known as 4-methylmethcathinone. It is regulated as a controlled substance because it is an analog of amphetamine (specifically, 4-methylmethamphetamine), which is included in Schedule III to the CDSA.

What is MDPV?

MDPV, also known as 3,4-methylenedioxypropylone, is a synthetic substance related to mephedrone. It is a potent stimulant.

Why is mephedrone scheduled and MDPV not?

Health Canada has not been aware of any widespread marketing or use in Canada of “bath salt” products containing MDPV and/or mephedrone. As there is no evidence of a significant presence of products containing MDPV in Canada, we are still collecting preliminary information. Mephedrone, meanwhile, is already a controlled substance in Canada as it has been deemed an analog of amphetamine which is listed under Schedule III to the CDSA.

DRAFT – March 5, 2012

How does MDPV fit into the criteria for scheduling?

CDSA Scheduling Factor	Preliminary Assessment of MDPV
International requirements and trends in control	<ul style="list-style-type: none"> Not controlled internationally. Preliminary analysis indicates that various levels of control have been placed on MDPV in the United States, United Kingdom, Denmark, Ireland, Finland and Sweden.
Chemical and/or pharmacological similarity to substances listed in CDSA	<ul style="list-style-type: none"> Structurally, MDPV appears to show some similarity to both mephedrone and amphetamine; further detailed analysis of the chemistry and pharmacology of MDPV needs to be conducted.
Legitimate therapeutic, scientific or industrial use	<ul style="list-style-type: none"> No drug products containing MDPV have been approved for sale in Canada. Preliminary research does not suggest any legitimate industrial or scientific uses
Potential for abuse and/or addiction liability	<ul style="list-style-type: none"> An assessment of the abuse and/or addiction liability of MDPV has yet to be conducted.
Evidence of extent of actual abuse	<ul style="list-style-type: none"> Media reports have emerged that MDPV is being used for its stimulant properties. However, no assessment has been conducted as of yet regarding the actual extent of abuse of MDPV in Canada.
Risk to personal and/or public health and safety	<ul style="list-style-type: none"> While little is known about the specific health effects of MDPV, the use of stimulants in general may significantly increase blood pressure, as well as heart and breathing rate. Their use has also been associated with severe panic attacks and anxiety, as well as hallucinations. DAS has identified MDPV and/or mephedrone in 332 exhibits tested since January 2010. DAS cannot verify, however, whether these samples are from "bath salt" products or from other street drugs.

*Phenmetrazine
Mephedrone*

*low percent
as slowly
increasing*

*serious &
Adverse
effects
- uncontrolled craving*

*Self-mutilation
Suicide
death*

after cessation

What is the Office of Controlled Substances (OCS) doing regarding the MDPV?

OCS worked with DAS and the Office of Research and Surveillance (CSTD) to confirm the scheduling status of mephedrone and MDPV and to gather preliminary information regarding the number of times they have been seized by law enforcement as suspected controlled substances. OCS remains in contact with the RCMP on this file and will consider developing a work plan regarding the potential scheduling of MDPV should intelligence suggest that the availability of MDPV and/or "bath salt" products warrants further action.



Re: bath salts 
Nathan Isotalo to: Tara Phillips

2012-03-08 01:34 PM

Hi Tara,

further to our discussion, it is my understanding that

-
- you would like me to begin gathering as much data on bath salts (mephedrone / MDPV) and;
 - you would like me to begin drafting an IAS in plain language also;
 - no deadline was given

Nathan.

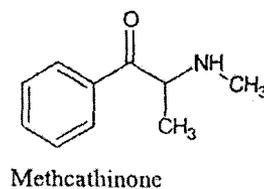
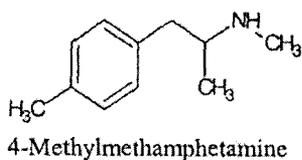
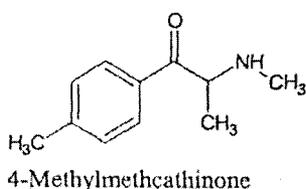
Tara Phillips

From: Tara Phillips/HC-SC/GC/CA To: Nathan I...

2012-03-08 11:24:52 AM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-03-08 11:24 AM
Subject: Can you pls come see me about bath salts when you have a minute?

Drug Status Report

Drug: 4-Methylmethcathinone**Drug Name Status:** 4-Methylmethcathinone is the common name**Other Names:** Mephedrone; 2-methylamino-1-p-tolylpropan-1-one**Chemical Name:** 2-Methylamino-1-(4-methylphenyl)-1-propanone**Chemical structure:****Molecular Formula:** C₁₁H₁₅NO**Pharmacological class / Application:** stimulant**International status:**

US: The substance is not currently listed on the US Controlled Substances Act and is not mentioned on the DEA website. However, 4-methylmethcathinone is controlled¹ in the US due to the analogue provisions in the CSA.

United Nations: The substance is not listed on the Yellow List - List of Narcotic Drugs under International Control nor the Green List - List of Psychotropic Substances under International Control.

Canadian Status: Item 1 of Schedule III to the CDSA is, "Amphetamines, their salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues." Although not listed specifically in item 1 of Schedule III, 4-methylmethamphetamine (structure above) is an amphetamine. 4-Methylmethcathinone is analogous to 4-methylmethamphetamine in that it contains the same structure with an additional oxygen. 4-Methylmethcathinone is therefore an analogue of 4-methylmethamphetamine and is included in item 1 of Schedule III to the CDSA.

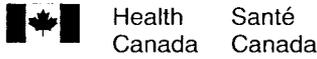
A similar rationale was used to recommend that 2-methylamino-1-(3,4-methylenedioxy)-propiophenone be included in item 1 of Schedule III. That report is appended for information.

¹ http://www.usdoj.gov/dea/programs/forensicsci/microgram/journal_v5_num14/pg1.html

The substance is also structurally similar to 2-methylamino-1-phenyl-1-propanone (methcathinone) which is listed as item 21 of Schedule III to the CDSA.

Recommendation: 4-Methylmethcathinone is included in item 1 of Schedule III to the CDSA and is a controlled substance.

June 19, 2008



STATUS DECISION OF CONTROLLED AND NON-CONTROLLED SUBSTANCE(S)

Substance: 3',4'-Methylenedioxy-alpha-pyrrolidinopentanophenone

Based on the current information available to the Office of Controlled Substances, it appears that the above substance is:

Controlled
Not Controlled

under the schedules of the *Controlled Drugs and Substances Act* (CDSA) for the following reason(s):

- 3',4'-Methylenedioxy-alpha-pyrrolidinopentanophenone shares a basic structural element with several controlled substances. These include cathinone, methcathinone, diethylpropion, phenmetrazine and pyrovalerone. The listings of these substances on the schedules to the CDSA are not extended by phrases that would include 3',4'-methylenedioxy-alpha-pyrrolidinopentanophenone.

Supporting document(s) attached: **X** (Drug Status Report by [redacted])

Prepared by: Xiao Peng Feng Date: June 27, 2006

s.19(1)

Drug Status Report by: [redacted] Date: June 27, 2006

Approved by: DIRECTOR, OFFICE OF CONTROLLED SUBSTANCES Date: _____

Drug Status Report

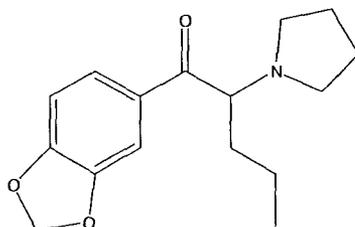
Drug: 3',4'-Methylenedioxy-alpha-pyrrolidinopentanophenone

Drug Name Status: 3',4'-methylenedioxy-alpha-pyrrolidinopentanophenone is the common name

Other Names: 3,4-Methylenedioxy-2-(1-pyrrolidinyl)valerophenone

Chemical Name: 1-(2H-benzo[3,4-d][1,3-dioxol-5-yl)-2-pyrrolidinylpentan-1-one

Chemical structure:



Molecular Formula: C₁₆H₂₁NO₃

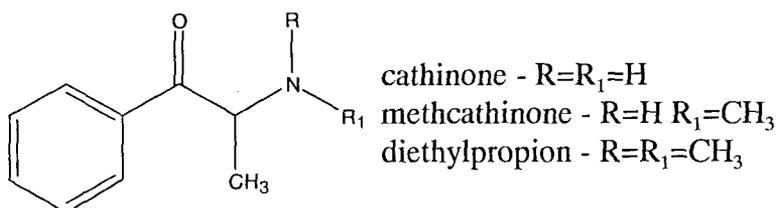
Pharmacological/chemical class / Application: unknown

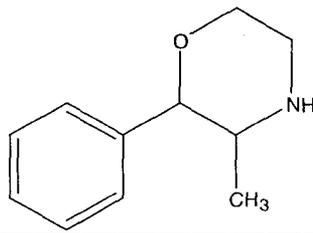
International status:

US: The substance is not listed on the US Controlled Substances Act and is not mentioned on the DEA website.

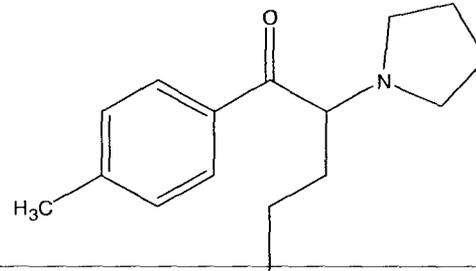
United Nations: The substance is not listed on the Yellow List - List of Narcotic Drugs under International Control nor the Green List - List of Psychotropic Substances under International Control.

Canadian Status: 3',4'-Methylenedioxy-alpha-pyrrolidinopentanophenone shares a basic structural element with several controlled substances. These include cathinone, methcathinone, diethylpropion, phenmetrazine and pyrovalerone.





Phenmetrazine



Pyrovalerone

The listings of these substances on the schedules to the CDSA are not extended by phrases that would include 3',4'-methylenedioxy-alpha-pyrrolidinopentanophenone.

Recommendation: 3',4'-Methylenedioxy-alpha-pyrrolidinopentanophenone is not included in the schedules to the CDSA and is not a controlled substance.

June 27, 2006

42

Journal of Pharmacology and Experimental Therapeutics

jpet.aspetjournals.org

Published online before print August 2, 2011, doi: 10.1124/jpet.111.184119

JPET August 2, 2011 jpet.111.184119

4-Methylmethcathinone(mephedrone): neuropharmacological effects of a designer stimulant of abuse

Gregory C Hadlock, Katy M Webb, Lisa M McFadden, Pei Wen Chu, Jonathan D Ellis, Scott C Allen, David M Andrenyak, Paula L Vieira-Brock, Christopher L German, Kevin M Conrad, Amanda J Hoonakker, James W Gibb, Diana G Wilkins, Glen R Hanson and Annette E Fleckenstein*

+ Author Affiliations

* Corresponding author; email: fleckenstein@hsc.utah.edu

Abstract

The designer stimulant, 4-methylmethcathinone (mephedrone), is among the most popular of the derivatives of the naturally occurring psychostimulant, cathinone. Mephedrone has been readily available for legal purchase both online and in some stores, and has been promoted by aggressive web-based marketing. Its abuse in many countries, including the United States, is a serious public health concern. Owing largely to its recent emergence, there are no formal pharmacodynamic or pharmacokinetic studies of mephedrone. Accordingly, the purpose of this study was to evaluate effects of this agent in a rat model. Results revealed that, similar to methylenedioxymethamphetamine, methamphetamine and methcathinone, repeated mephedrone injections (4 x 10 - 25 mg/kg/injection, s.c., 2-h intervals, administered in a pattern used frequently to mimic psychostimulant "binge" treatment) cause a rapid decrease in striatal dopamine (DA) and hippocampal serotonin (5-hydroxytryptamine; 5HT) transporter function. Mephedrone also inhibited both synaptosomal DA and 5HT uptake. Like methylenedioxymethamphetamine, but unlike methamphetamine or methcathinone, repeated mephedrone administrations also caused persistent serotonergic, but not dopaminergic, deficits. However, mephedrone caused DA release from a striatal suspension approaching that of methamphetamine, and was self-administered by rodents. A method was developed to assess mephedrone concentrations in rat brain and plasma, and mephedrone levels were determined 1 h after a "binge" treatment. These data demonstrate that mephedrone has a unique pharmacological profile with both abuse liability and neurotoxic potential.

amphetamine dopamine drug abuse neurotransmitters serotonin toxicology

Received May 18, 2011.
Revision received July 22, 2011.
Accepted July 26, 2011.

The American Society for Pharmacology and Experimental Therapeutics



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- [Healthy Minds and Bodies \(29\)](#)
- [National Drug Facts Week \(25\)](#)
- [News & Events \(55\)](#)
- [Prescription Drug Abuse \(12\)](#)
- [Real Teens Ask About Drugs \(25\)](#)
- [Real-Life Stories \(4\)](#)
- [What Do You Think? \(27\)](#)
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- [March 2012](#)
- [February 2012](#)
- [January 2012](#)

- [December 2011](#)
- [November 2011](#)
- [October 2011](#)
- [September 2011](#)
- [August 2011](#)
- [July 2011](#)
- [June 2011](#)
- [May 2011](#)
- [April 2011](#)
- [March 2011](#)
- [February 2011](#)
- [January 2011](#)
- [December 2010](#)
- [November 2010](#)
- [October 2010](#)
- [September 2010](#)
- [August 2010](#)
- [July 2010](#)
- [June 2010](#)
- [May 2010](#)
- [April 2010](#)
- [March 2010](#)
- [February 2010](#)
- [January 2010](#)
- [December 2009](#)
- [November 2009](#)
- [October 2009](#)
- [September 2009](#)
- [August 2009](#)
- [July 2009](#)
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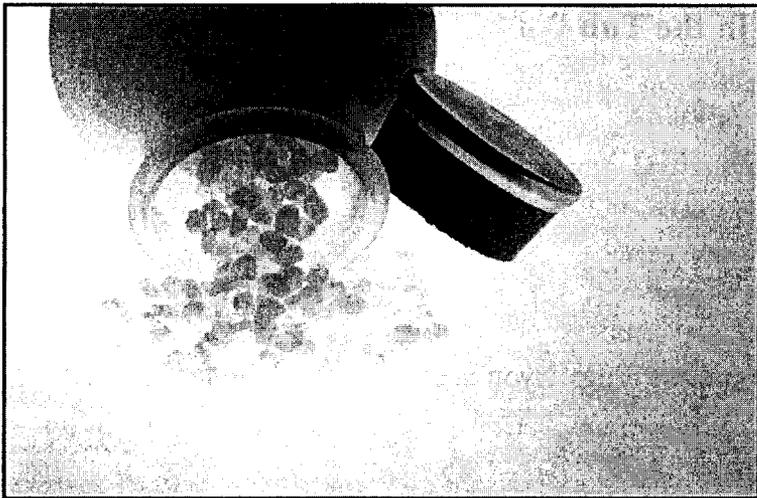
Keep "Bath Salts" in the Tub



Rating: 4.1/5 (12 votes cast)



18 Comments



Bath salts. The name sounds innocent enough, like an old-fashioned cure for tired feet. But these days, "bath salts" aren't just found in your local soap aisle at the grocery store or day spa—bath salts are now being used as a type of drug. Some are now laced with synthetic stimulants, which people use to get high by swallowing, snorting or injecting them. And...they have just been made illegal.

What Are Bath Salts?

Because these drugs are relatively new and for now unregulated by the U.S. Drug Enforcement Agency (DEA), scientists are not exactly sure of the ingredients in each brand. We do know that the chemicals in these bath salts mimic the effects of amphetamines—stimulants like cocaine or meth—such as racing heart, increased blood pressure and body temperature, and even seizures, which have brought many people to emergency rooms across the country.

According to the head of the Louisiana Poison Center, at least 84 people in that state have been hospitalized after getting high from bath salts. Nationwide, more than 4,000 calls about bath salts have come in to poison centers during the first 7 months of 2011—up from 303 calls in all of 2010.

Keep “Bath Salts” in the Tub

Risks

It is too early to tell what the exact short- and long-term effects from abusing bath salts is, but what little we do know so far is alarming enough. Effects can include extreme paranoia, hallucinations, and suicidal thoughts, as well as chest pains, soaring blood pressure, and rapid heartbeat. A number of deaths were reported in people who took the drug, including at least one possible suicide.

Several states, including Hawaii, Louisiana, and Michigan, have introduced laws to ban bath salts. The DEA just announced it will make selling or possessing these chemicals illegal for a year while they study them further. SBB will keep you posted on what they learn.

If anyone offers you bath salts as a way to get high, let them know not only are they taking big risks, they are also doing something illegal.

Bookmark and Share 

Posted: Friday, September 16 2011 Author: admin

Tags: [amphetamines](#), [bath salts](#), [stimulants](#)

Category: [Drug Facts](#)

18 Responses to “ Keep “Bath Salts” in the Tub ”

1. *tgrd* says:

[October 19, 2011 at 3:45 pm](#)

wow thats not good

2. *kush* says:

[November 1, 2011 at 10:30 am](#)

why don't you people tell the high's from these drugs...you need to have all the facts

3. *Anonymous* says:

[November 10, 2011 at 9:54 pm](#)

it's just so scary because you don't know what will happen next. you don't know what the dealers will offer to make a quick dollar off some stupid kid. This makes you think about how times have changed; at one point bath salts were made to make your skin smooth and feel good. now they're making it to practically kill.

4. *denenenenenenene bathman* says:

[November 11, 2011 at 9:37 pm](#)

wow, thats really not good

5. *someone* says:

[November 12, 2011 at 3:50 pm](#)

you know when poeple use bath salts they dont actually realize what they are doing to their body. they are killing all of their organs in thier body. any type of drug poeple use, they are killing brain cells. im pretty sure poeple dont want to die from making the wrong decision.

6. *Virginia Dui* says:
November 13, 2011 at 9:51 pm

Getting a [commercial link removed, per guidelines] DUI could be bad but getting hooked on Bath Salts is worse. If you are crazy enough to take this terrible drug you will be asking for trouble. Living in Maine i have seen people go crazy on this stuff. By the way it is not the "bath salts" at the store. It's a drug that is a derivative of meth. Bad stuff stay away!

7. *Meeeee* says:
November 14, 2011 at 9:48 pm

that stinks. I have to read this for health class but i hate reading these things because i get so... uneasy when I hear about these things. Its like, 'wow does everyone abuse drugs? what kind of a place do we live in?' ehhhh.

8. *bad* says:
November 16, 2011 at 5:26 pm

I was offered this drug recently at a smoke shop as legal and to mix in my drink. Thinking it was legal, I assumed it was not that bad for me. After blacking out from this drug I was sick for 4 days. DO NOT TRY THIS!!

9. *code breaker* says:
November 29, 2011 at 10:35 am

i youst to use bath salt untell now hahahahahahahah [obscenity removed, per guidelines]

10. *Deceased friends son* says:
November 29, 2011 at 8:08 pm

last night I got a call from my daughter(she and my friends son were raised very close together, as we were friends so were they) she called to tell me that he had committed suicide, then went on to tell me that he had been using this stuff they call "BATHTUB SALTS" he hung himself. What an awful way to go!

11. *Addict!!* says:
December 6, 2011 at 8:03 pm

I have to agree I am a recovering addict and I believe these so called bath salts needs to be banned and made illegal!! Not just to protect our children but to help those of us trying to be clean and drug free!!! Thank u

12. *Meg* says:
December 25, 2011 at 8:27 pm

OMG I had no idea! 😬 but what if they come from a legal store? I brought body lotion and body gel and it came with bath salts. I looked at the ingredients they are not bad but I am still unsure if I should use bath salts. 😬 they smelled so good..

13. *IM AWESOME* says:
January 10, 2012 at 8:23 am

really they use bath salts for drugs?! what next ketchup?

14. *prettygrl* says:
[January 10, 2012 at 8:26 am](#)

i have to read this in my health class and it's horrible

15. *Molly* says:
[January 17, 2012 at 12:33 am](#)

Are these "bath salts" something that may be in the scented fizzy bath bombs that I use in the tub? If they gave a woman a flesh eating bacteria through a puncture wound, I don't want to know what could happen to my private parts that sit in the bath water! Hopefully this is a different chemical altogether.

16. *NIDAminds* says:
[February 2, 2012 at 10:19 am](#)

@Molly Don't worry, they are totally different.

17. *NIDAminds* says:
[February 2, 2012 at 11:28 am](#)

@Meg What a great question! The "bath salts" discussed on our blog are not the same type that you typically find in your bath and body aisle. As long as you use your bath salts in your bath water and don't ingest, snort or inject them, you'll be fine. Enjoy your bath!

18. *did it!* says:
[February 13, 2012 at 2:05 am](#)

this literately aint no joke it changes people

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Synthetic Drugs (a.k.a. K2, Spice, Bath Salts, etc.)

Synthetic Drugs

Overview and History

- Synthetic marijuana (often known as “K2” or “Spice”) and bath salts products are often sold in legal retail outlets as “herbal incense” and “plant food,” respectively, and labeled “not for human consumption” to mask their intended purpose and avoid FDA regulatory oversight of the manufacturing process.
- Synthetic marijuana consists of plant material that has been laced with substances (synthetic cannabinoids) that users claim mimics Δ9-tetrahydrocannabinol(THC), the primary psychoactive active ingredient in marijuana, and are marketed toward young people as a “legal” high.
- Use of synthetic marijuana is alarmingly high. According to data from the 2011 Monitoring the Future survey of youth drug-use trends, 11.4 percent of 12th graders used Spice or K2 in the past year, making it the second most commonly used illicit drug among seniors.
- Bath salts contain manmade chemicals related to amphetamines that often consist of methylenedioxypropylvalerone (MDPV), mephedrone, and methylone, also known as substituted cathinones.
- The Administration has been working over the past 24 months with Federal, Congressional, State, local, and non-governmental partners to put policies and legislation in place to combat this threat, and to educate people about the tremendous health risk posed by these substances.

A Rapidly Emerging Threat

1. Ann Emerg Med. 2012 Mar 2. [Epub ahead of print]

Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypropylone.

Borek HA, Holstege CP.

Division of Medical Toxicology, Department of Emergency Medicine, University of Virginia School of Medicine, Charlottesville, VA.

"Bath salts" are being increasingly used as drugs of abuse. These products have been found to contain a variety of compounds, including 3,4-methylenedioxypropylone (MDPV). We present a case of a 25-year-old man who injected bath salts and acutely developed severe agitation, hyperthermia, and tachycardia. Despite aggressive early medical management, including dialysis, he progressed to multiorgan system failure, although he ultimately recovered after a prolonged hospital course. The only chemical substance detected on comprehensive toxicologic testing was MDPV, a synthetic cathinone analogue. According to our case, MDPV abuse may result in adverse multisystem organ effects, including rhabdomyolysis, cardiac injury, hepatic injury, and renal failure. It is unknown whether these end-organ effects were due to direct cellular toxicity induced by MDPV or a result of the patient's marked agitation and hyperthermia. Acute management should focus on the rapid identification of organ injury and appropriate supportive care.

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PMID: 22387085 [PubMed - as supplied by publisher]

2. J Miss State Med Assoc. 2011 Dec;52(12):375-7.

Illicit bath salts: not for bathing.

Kyle PB, Iverson RB, Gajagowni RG, Spencer L.

Department of Pathology, University of Mississippi Medical Center, Jackson, MS 39216, USA. pkyle@umc.edu

affected
Mississippi
BACKGROUND: There has been an increase in the popularity of designer drugs known as "Bath Salts" in the United States. These products commonly contain mephedrone, mephylone, methylenedioxypropylone (MDPV), or other cathinone derivatives with psychoactive properties similar to amphetamine and cocaine. Although recently outlawed, abuse of these products continues to occur in Mississippi.
METHODS: We report a 19-year-old male who presented with paranoia and auditory as well as visual hallucinations. Auditory effects included voices that prompted him to kill people. The patient displayed anxiety, paranoia, and exhibited repeated bouts of inappropriate laughter. Urine toxicology analysis via GC/MS detected MDPV, a compound structurally similar to methylenedioxymethamphetamine (MDMA).
CONCLUSIONS: Clinicians should be aware that these designer drugs are not detected with common immunoassay drug screens. Symptoms most commonly associated with these substances include tachycardia, delusions, hallucinations, and paranoia. Psychosis, self-harm, and death have been associated with some cases.

PMID: 22329114 [PubMed - in process]

3. J Med Toxicol. 2012 Mar;8(1):69-75.

Death Following Recreational Use of Designer Drug "Bath Salts" Containing 3,4-Methylenedioxypropylvalerone (MDPV).

Murray BL, Murphy CM, Beuhler MC.

Department of Emergency Medicine, Carolinas Medical Center, PO Box 32861, MEB 3rd Floor, Charlotte, NC, 28232, USA.

INTRODUCTION: 3,4-Methylenedioxypropylvalerone (MDPV) is a designer stimulant drug that has gained popularity in the USA. Although adverse effects of MDPV have been described, to our knowledge, this is the first reported death.

CASE REPORT: We report the case of a 40-year-old male who injected and snorted "bath salts" containing MDPV and subsequently became agitated, aggressive, and experienced a cardiac arrest. He was resuscitated after his initial arrest; however, he developed hyperthermia, rhabdomyolysis, coagulopathy, acidosis, anoxic brain injury, and subsequently died.

DISCUSSION: This is the first case in the medical literature to report death due to isolated confirmed MDPV intoxication. The manner of death is also consistent with excited delirium syndrome.

PMID: 22271565 [PubMed - in process]

4. Ann Emerg Med. 2012 Jan 9. [Epub ahead of print]

Serotonin Syndrome Associated With MDPV Use: A Case Report.

Mugele J, Nañagas KA, Tormoehlen LM.

Indiana University School of Medicine, Indianapolis, IN.

Serotonin syndrome is associated with use of certain street drugs, including methamphetamine, cocaine, and ecstasy. We describe a case of a woman who developed clinical findings consistent with serotonin syndrome after insufflation of 3,4-methylenedioxypropylvalerone (MDPV), a synthetic amphetamine. MDPV belongs to a group of substances called phenylethylamines, which are β -ketone analogs of other drugs of abuse, such as amphetamines and 3,4-methylenedioxymethamphetamine. She also received fentanyl initially during her hospitalization, which has also been associated with serotonin syndrome. In addition to benzodiazepines and supportive care, she was treated with cyproheptadine for 8 days, with slow resolution of her symptoms.

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PMID: 22237165 [PubMed - as supplied by publisher]

5. Orv Hetil. 2011 Dec 11;152(50):2010-9.

[3,4-methylene-dioxy-pyrovalerone (MDPV) epidemic?].

[Article in Hungarian]

Kalapos MP.

Elméleti Biológiai Kutatócsoport Budapest Józsefvárosi Egészségügyi Szolgálat VIII. Támasz Gondozó Budapest Korányi S. u. 3/A 1089. mpkalapos@freemail.hu

Little is known about 3,4-methylene-dioxy-propylvalerone (MDPV), a new designer drug that has become popular in Hungary in the last couple of months. At the same

time, its consumption, as a consequence of its low street-price rises so fast that the event can be considered an epidemic. This paper reviews the chemistry, biochemistry and metabolism of MDPV. Then, on the basis of a few international reports and the author's own clinical observations, it discusses MDPV intoxication and withdrawal. In the metabolism of MDPV, the most important catalyst is the CYP2C19 isoenzyme, but the CYP1A2 and the CYP2D6 isoenzymes also play a crucial role. The formed catechols are conjugated with either glucuronic acid or sulfate. It is important to note that MDPV is consumed either together or in a sequence with other illicit drugs of abuse. As far as it can be established, MDPV use increases the activity and vigilance, decreases appetite and claim to sleep, but it can also provoke cardiac sensations and disturbance of perception. In the course of coming down, withdrawal after MDPV use, bone and muscle pain, hypersomnia, disturbance of vision are experienced, but panic attack may also occur. The appearance of new designer drugs on the market draws attention to a need of paradigm changing in spiritual field. Unless it happens these negative trends likely will speed up.

PMID: 22112374 [PubMed - indexed for MEDLINE]

6. J Med Toxicol. 2012 Mar;8(1):33-42.

The toxicology of bath salts: a review of synthetic cathinones.

Prosser JM, Nelson LS.

Weill Cornell Medical Center, New York, NY, USA, jprosser100@gmail.com.

Synthetic cathinones have recently emerged and grown to be popular drugs of abuse. Their dramatic increase has resulted in part from sensationalized media attention as well as widespread availability on the Internet. They are often considered "legal highs" and sold as "bath salts" or "plant food" and labeled "not for human consumption" to circumvent drug abuse legislation. Cathinone is a naturally occurring beta-ketone amphetamine analogue found in the leaves of the *Catha edulis* plant. Synthetic cathinones are derivatives of this compound. Those that are being used as drugs of abuse include butylone, dimethylcathinone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, mephedrone, methedrone, methylenedioxypropylone (MDPV), methylone, and pyrovalerone. Synthetic cathinones are phenylalkylamines derivatives, and are often termed "bk-amphetamines" for the beta-ketone moiety. They may possess both amphetamine-like properties and the ability to modulate serotonin, causing distinct psychoactive effects. Desired effects reported by users of synthetic cathinones include increased energy, empathy, openness, and increased libido. Cardiac, psychiatric, and neurological signs and symptoms are the most common adverse effects reported in synthetic cathinone users who require medical care. Deaths associated with use of these compounds have been reported. Exposure to and use of synthetic cathinones are becoming increasingly popular despite a lack of scientific research and understanding of the potential harms of these substances. The clinical similarities to amphetamines and MDMA specifically are predictable based on the chemical structure of this class of agents. More work is necessary to understand the mechanisms of action, toxicokinetics, toxicodynamics, metabolism, clinical and psychological effects as well as the potential for addiction and withdrawal of these agents.

PMID: 22108839 [PubMed - in process]

7. Drug Test Anal. 2011 Nov 18. doi: 10.1002/dta.358. [Epub ahead of print]

Identification of ten new designer drugs by GC-MS, UPLC-QTOF-MS, and NMR as part

of a police investigation of a Danish Internet company.

Reitzel LA, Dalsgaard PW, Müller IB, Cornett C.

University of Copenhagen, Department of Forensic Medicine, Copenhagen, Denmark.
lotte.reitzel@forensic.ku.dk.

The ability of forensic laboratories to detect and identify unknown compounds is highly important since new, non-controlled designer drugs are appearing on the market with increasing frequency. In this study, the combined use of gas chromatography-mass spectrometry (GC-MS) and ultra performance liquid chromatography-quadrupole time of flight-mass spectrometry (UPLC-QTOF-MS) was used for screening of new unknowns. In one large seizure from a Danish Internet company, ten different drugs were identified. Several of the compounds were seized for the first time in Denmark. The GC-MS and UPLC-QTOF-MS analyses were supplemented by nuclear magnetic resonance (NMR) spectra for the structural elucidation of p-fluoroamphetamine, mephedrone (4-methylmethcathinone), flephedrone (4-fluoromethcathinone), PPP (α -pyrrolidinopropiophenone), MDPV (3,4-methylenedioxypropylvalerone), Bk-MBDB (2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one), pFBT (3-(pfluorobenzoyl)-tropane), and JWH-073 (1-butyl-3-(1-naphthoyl)indol), whereas methylone (3,4-methylenedioxymethcathinone) and N-ethylcathinone matched electron impact-mass spectrometry (EI-MS) library spectra and therefore the screenings were considered sufficient. EI-MS spectra and the proposed main fragmentation patterns are presented as well as QTOF-MS exact masses and fragments and NMR chemical shifts. For the β -ketophenylethylamines (mephedrone, flephedrone, PPP, MDPV, Bk-MBDB, methylone, and N-ethylcathinone) some general fragmentation patterns observed in the EI-MS and QTOF-MS spectra are further discussed and compared to other β -ketophenylethylamines. Copyright © 2011 John Wiley & Sons, Ltd.

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PMID: 22102551 [PubMed - as supplied by publisher]

8. Emerg Med J. 2011 Dec;28(12):1068-70.

Energy-1 ('NRG-1'): don't believe what the newspapers say about it being legal.

Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, Dargan PI.

Clinical Toxicology Service, Guy's and St Thomas' NHS Foundation Trust and King's Health Partners, London, UK. david.wood@gstt.nhs.uk

A 31-year-old man purchased the legal high Energy-1 (NRG-1) over the internet; this was advertised as containing the compound naphthylpyrovalerone (NPV), which at the time was currently legally available in the UK. He ingested 1 g of this substance and developed a prolonged high associated with palpitations, sweating and insomnia. Analysis of both the powder and serum samples from the patient demonstrated that he ingested two classified recreational drugs β -keto-N-methylbenzodioxolylpropylamine (butylone) and methylenedioxypropylvalerone (MDPV) rather than the legal substance NPV. Users of legal highs need to be aware that legal highs purchased over the internet may contain illegal substances and therefore they may be liable for prosecution if found in possession of these substances. Future educational campaigns aimed at recreational drug and legal high users should include reference to the potential legal implications of buying these substances.

PMID: 22101594 [PubMed - indexed for MEDLINE]

000204

9. Fed Regist. 2011 Oct 21;76(204):65371-5.

→ Schedules of controlled substances: temporary placement of three synthetic cathinones in Schedule I. Final Order.

Drug Enforcement Administration, Department of Justice.

The Administrator of the Drug Enforcement Administration (DEA) is issuing this final order to temporarily schedule three synthetic cathinones under the Controlled Substances Act (CSA) pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). The substances are 4-methyl-N-methylcathinone (mephedrone), 3,4-methylenedioxy-N-methylcathinone (methydone), and 3,4-methylenedioxypropylvalerone (MDPV). This action is based on a finding by the Administrator that the placement of these synthetic cathinones and their salts, isomers, and salts of isomers into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. As a result of this order, the full effect of the CSA and its implementing regulations including criminal, civil and administrative penalties, sanctions and regulatory controls of Schedule I substances will be imposed on the manufacture, distribution, possession, importation, and exportation of these synthetic cathinones.

PMID: 22016903 [PubMed - indexed for MEDLINE]

10. Toxicol Lett. 2012 Jan 5;208(1):12-5. Epub 2011 Oct 8.

3,4-methylenedioxypropylvalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online.

Coppola M, Mondola R.

Department of Addiction, ASL CN2, Viale Coppino 46, 12051, Alba (CN), Italy.
coppolamail@alice.it

The illicit marketplace of substances of abuse continually offers for sale legal alternatives to controlled drugs to a large public. In recent years, a new group of designer drugs, the synthetic cathinones, has emerged as a new trend, particularly among young people. The 3,4-methylenedioxypropylvalerone (MDPV), one of this synthetic compounds, caused an international alert for its cardiovascular and neurological toxicity. This substance, sold as bath salts, has caused many serious intoxications and some deaths in several countries. The aim of this paper is summarise the clinical, pharmacological and toxicological information about this new designer drug.

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PMID: 22008731 [PubMed - indexed for MEDLINE]

11. Drug Test Anal. 2011 Sep;3(9):569-75. doi: 10.1002/dta.204. Epub 2010 Dec 29.

Analysis of NRG 'legal highs' in the UK: identification and formation of novel cathinones.

Brandt SD, Freeman S, Sumnall HR, Measham F, Cole J.

School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, UK. s.brandt@ljmu.ac.uk

A large number of cathinone derivatives have shown a wide range of bioactive properties, attracting great interest from communities associated with pharmaceutical research. Some of these derivatives have gained popularity as so-called recreational 'legal highs' due to their availability on the Internet and high street shops. A previous study described the qualitative analysis of 24 'legal high' Energy-1 (NRG-1) and NRG-2 products obtained from 18 websites following the ban on mephedrone and derivatives in April 2010. The majority of these products contained a mixture of cathinones just carrying a new label. Here, three additional cathinone products have been detected; two from an NRG-1 sample and one from an NRG-3 sample. This report describes their identification. NRG-1 sample 1 consisted of a mixture of 4 cathinones namely 4-fluoromethcathinone (1), 1-(3,4-methylenedioxyphenyl)-2-(methylamino)pentan-1-one (pentylone, 2), 3,4-methylenedioxy- α -pyrrolidinobutyrophenone (MDPBP, 3) and 3,4-methylenedioxyprovalerone (MDPV, 4). The sample labelled as NRG-3 (mislabeled with the chemical structure of mephedrone) consisted of a mixture of 4-methyl- α -pyrrolidinopropiophenone (MPPP, 5) and (2), whereas the remaining NRG-1 sample 2 (also mislabeled with the chemical structure of mephedrone) consisted of a mixture of (2) and (3). Qualitative analyses were carried out by GC-(EI/CI)-MS, NMR spectroscopy and confirmation by preparation of standards. The preparation of brominated precursors carrying the 3,4-methylenedioxyphenyl nucleus revealed extensive α,α -dibromination: the mass spectral and NMR data of these intermediates are also presented and discussed.

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PMID: 21960541 [PubMed - indexed for MEDLINE]

12. Forensic Sci Int. 2012 Mar 10;216(1-3):19-28. Epub 2011 Sep 9.

The analysis of substituted cathinones. Part 3. Synthesis and characterisation of 2,3-methylenedioxy substituted cathinones.

Kavanagh P, O'Brien J, Fox J, O'Donnell C, Christie R, Power JD, McDermott SD.

Department of Pharmacology and Therapeutics, School of Medicine, Trinity Centre for Health Science, St. James Hospital, Dublin 8, Ireland.

The first synthesis of the 2,3-isomers of MDPV, butylone and methylone is reported. The isomers were characterised by ^1H and ^{13}C NMR spectroscopy and compared to the corresponding 3,4-isomers. A GC method is described which separates the 3,4- and the 2,3-isomers from each other. IR spectra of the 2,3-isomers are also compared with the corresponding 3,4-isomers. Two seized drug samples were analysed by GCMS and the samples were found to contain the 3,4-isomers.

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PMID: 21907509 [PubMed - in process]

13. Clin Toxicol (Phila). 2011 Jul;49(6):499-505.

Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States.

Spiller HA, Ryan ML, Weston RG, Jansen J.

Kentucky Regional Poison Center, Louisville, KY 40232-5070, USA.

henry.spiller@nortonhealthcare.org

Recently, there has been a worldwide rise in the popularity and abuse of synthetic cathinones. In 2009 and 2010, a significant rise in the abuse of a new group of synthetic cathinones was reported in Western Europe. In 2010, the rapid emergence of a new drug of abuse, referred to as bath salts or "legal high," occurred in the USA. The growing number of cases along with the alarming severity of the effects caused by the abuse of these substances prompted significant concern from both healthcare providers and legal authorities. We report the experience of the first 8 months of two regional poison centers after the emergence of a new group of substances of abuse. METHOD: This was a retrospective case series of patients reported to two poison centers with exposures to bath salts. Additionally, 15 "product samples" were obtained and analyzed for drug content using GC/MS.

RESULTS: There were 236 patients of which 184 (78%) were male. Age range was 16-64 years (mean 29 years, SD 9.4). All cases were intentional abuse. There were 37 separate "brand" names identified. Clinical effects were primarily neurological and cardiovascular and included: agitation (n = 194), combative behavior (n = 134), tachycardia (n = 132), hallucinations (n = 94), paranoia (n = 86), confusion (n = 83), chest pain (n = 40), myoclonus (n = 45), hypertension (n = 41), mydriasis (n = 31), CPK elevations (n = 22), hypokalemia (n = 10), and blurred vision (n = 7). Severe medical outcomes included death (n = 1), major (n = 8), and moderate (n = 130). Therapies included benzodiazepines (n = 125), antipsychotics (n = 47), and propofol (n = 10). Primary dispositions of patients were: 116 (49%) treated and released from ED, 50 (21%) admitted to critical care, 29 (12%) admitted to psych, and 28 (12%) lost to follow up. Nineteen patients had blood and/or urine analyzed using GC/MS. MDPV was detected in 13 of 17 live patients (range 24-241 ng/mL, mean 58 ng/mL). The four samples with no drug detected, reported last use of bath salts >20 h prior to presentation. Three of five patients had MDPV detected in urine (range 34-1386 ng/mL, mean 856 ng/mL). No mephedrone or methylone was detected in any sample. Quantitative analysis performed on postmortem samples detected MDPV in blood at 170 ng/mL and in urine at 1400 ng/mL. No other synthetic cathinones were detected.

DISCUSSION: This is the first report of MDPV exposures with quantitative blood level confirmation. Clinical effects displayed a sympathomimetic syndrome, including psychotic episodes often requiring sedation, movement disorders, and tachycardia. Within 8 months of their appearance, 16 states had added synthetic cathinones to the controlled substances list as a Schedule I drug.

CONCLUSION: We report the emergence of a new group of substances of abuse in the USA, known as bath salts, with quantitative results in 18 patients. State and federal authorities used timely information from poison centers on the bath salt outbreak during investigations to help track the extent of use and the effects occurring from these new drugs. Close collaboration between state authorities and poison centers enhanced a rapid response, including legislation.

PMID: 21824061 [PubMed - indexed for MEDLINE]

14. Gen Hosp Psychiatry. 2011 Sep-Oct;33(5):525-6. Epub 2011 Jul 16.

Hallucinatory delirium following use of MDPV: "Bath Salts".

Penders TM, Gestring R.

Department of Psychiatry, Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA. penderst@ecu.edu

PMID: 21762997 [PubMed - indexed for MEDLINE]

15. Drug Test Anal. 2011 Jul-Aug;3(7-8):496-504. doi: 10.1002/dta.306. Epub 2011 Jun 11.

Development of a rapid LC-MS/MS method for direct urinalysis of designer drugs.

Bell C, George C, Kicman AT, Traynor A.

Department of Forensic Science and Drug Monitoring, Kings College London, School of Biomedical and Health Sciences, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK.

The current immunoassay screening methodologies used to detect sympathomimetic amines within the context of workplace drug testing may fail to detect a number of the emerging designer drugs, for example β -keto amphetamines and piperazine derivatives, commonly referred to as 'legal highs'. Therefore, a rapid multi-analyte qualitative screening method, using ultra-high-pressure liquid chromatography-tandem mass spectrometry (LC-MS/MS), was investigated for analysis of new designer drugs that have emerged from the former legal highs market. Eight analytes were targeted as model compounds: 4-methylmethcathinone (mephedrone), 3,4-methylenedioxymethcathinone (bk-MDMA, 'methyldrone'), 2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one (bk-MBDB, 'butylone'), 4-methoxymethcathinone (bk-PMMA, 'methedrone'), 1-benzylpiperazine (BZP), 1-(3-trifluoromethyl phenyl)-piperazine (TFMPP), 1-(3-chloro phenyl)-piperazine (mCPP), and 3,4-methylenedioxypyrovalerone (MDPV). The LC-MS/MS method developed encompassed direct analysis following a 1:4 dilution of urine with mobile phase to reduce matrix effects. Although not all compounds were completely resolved chromatographically, two product ions conferred sufficient specificity to allow target analyte identification. Although all target analytes were readily detected at 500 ng/ml, a cut-off of 1000 ng/ml was chosen to mirror the amphetamine screening cut-off commonly used for routine analysis of workplace drug testing samples. In conclusion, direct analysis using LC-MS/MS offers an attractive way forward for the development of a rapid routine screen for new psychoactive substances, particularly given the growing number of novel compounds.

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PMID: 21744513 [PubMed - indexed for MEDLINE]

16. MMWR Morb Mortal Wkly Rep. 2011 May 20;60(19):624-7.

Emergency department visits after use of a drug sold as "bath salts"--Michigan, November 13, 2010-March 31, 2011.

Centers for Disease Control and Prevention (CDC).

Collaborators: Benzie F, Hekman K, Cameron L, Wade DR, Miller C, Smolinske S, Warrick B.

On February 1, 2011, in response to multiple news reports, the Michigan Department of Community Health (MDCH) contacted the Children's Hospital of Michigan Poison Control Center (PCC) regarding any reports of illness in the state caused by the use of recreational designer drugs sold as "bath salts." Unlike traditional cosmetic bath salts, which are packaged and sold for adding to bath water for soaking and cleaning, the drugs sold as "bath salts" have no legitimate use for bathing and are intended for substance abuse. These products can contain stimulant compounds such as 3,4-methylenedioxypyrovalerone (MDPV) or 4-methylmethcathinone (mephedrone). The PCC told MDCH that, earlier in the day, the PCC had learned that numerous persons had visited the local emergency department (ED) in Marquette County with cardiovascular and neurologic signs of

acute intoxication. This report summarizes the subsequent investigation, which identified 35 persons who had ingested, inhaled, or injected "bath salts" and visited a Michigan ED during November 13, 2010-March 31, 2011. Among the 35 patients, the most common signs and symptoms of toxicity were agitation (23 patients [66%]), tachycardia (22 [63%]), and delusions/hallucinations (14 [40%]). Seventeen patients were hospitalized, and one was dead upon arrival at the ED. The coordinated efforts of public health agencies, health-care providers, poison control centers, and law enforcement agencies enabled rapid identification of this emerging health problem. Mitigation of the problem required the execution of an emergency public health order to remove the toxic "bath salts" from the marketplace. Lessons from the Michigan experience could have relevance to other areas of the United States experiencing similar problems.

PMID: 21597456 [PubMed - indexed for MEDLINE]

17. Forensic Sci Int. 2011 Jul 15;210(1-3):213-20. Epub 2011 Apr 16.

Identification and characterization of the new designer drug 4'-methylethcathinone (4-MEC) and elaboration of a novel liquid chromatography-tandem mass spectrometry (LC-MS/MS) screening method for seven different methcathinone analogs.

Jankovics P, Váradi A, Tölgyesi L, Lohner S, Németh-Palotás J, Koszegi-Szalai H.

National Institute of Pharmacy, Zrínyi u. 3., PO Box 450, H-1051 Budapest, Hungary. jankovics.peter@ogyi.hu

A fast and simple LC-MS/MS method was developed for screening mephedrone, butylone, methylenedioxypropylone (MDPV), flephedrone, methylone and methedrone in bulk powder samples. Samples were separated on a reverse phase column using gradient elution with mixtures of water, acetonitrile and formic acid. After optimization a limit of detection of about 2ngmL(-1) was achieved using multiple reaction monitoring (MRM) mode. Total run time was less than 8min. Typical fragmentation characteristics of the studied compounds are discussed. The method was successfully applied to several unknown bulk powder samples seized by the Hungarian Customs and Finance Guard. One of the samples contained the new designer drug 4'-methylethcathinone (4-MEC), which was identified and characterized by LC-MS/MS, NMR, FT-IR and LC-TOF-MS techniques. The method is also deemed to be applicable for the screening of simple dosage forms such as tablets and capsules.

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PMID: 21498012 [PubMed]

18. Forensic Sci Int. 2011 Jul 15;210(1-3):195-200. Epub 2011 Apr 7.

New designer drug of abuse: 3,4-Methylenedioxypropylone (MDPV). Findings from apprehended drivers in Finland.

Kriikku P, Wilhelm L, Schwarz O, Rintatalo J.

Vita Health Care Services Ltd., Vita Laboratory, Laivakatu 5 F, 00150 Helsinki, Finland. pirkko.kriikku@vita.fi

Starting in 2008 a new designer drug, 3,4-methylenedioxypropylone (MDPV) appeared among users of illegal drugs in Finland. Since then there have been several seizures of MDPV by police and customs and it has been connected to many

crimes of different types. In this study the incidence and impact of the use of MDPV in drivers suspected of being under the influence of drugs (DUID) in Finland was assessed. Since autumn 2009, blood samples from drivers suspected of DUID in Finland have been analysed for the presence of MDPV. A new LC-MS/MS method for the determination of MDPV in serum was established. In order to assess the impact of MDPV on driving performance, drug and alcohol findings of positive MDPV cases were compared with data from the clinical examination carried out while the suspect was under arrest. In a period of one year there were 259 positive MDPV cases from apprehended drivers (5.7% of all confirmed DUID cases). In 80% of the cases in which MDPV was found, amphetamine was also present. Benzodiazepines were also frequently found together with MDPV, which was to be expected since in Finland, in our experience, stimulants are very often used together with benzodiazepines. In most cases it remained unclear whether the observed psycho-physical achievement deficiency was induced by MDPV because the concentrations of other drugs, especially other stimulants, were often high. However, in some subjects, MDPV, or MDPV in combination with other substances was the most probable cause of the impairment. The concentrations of MDPV varied from 0.016mg/L to over 8.000mg/L. Little is known about the pharmacology of MDPV. However, based on our findings it is clear that MDPV has a serious impact on traffic safety in Finland.

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PMID: 21477955 [PubMed - indexed for MEDLINE]

19. Forensic Sci Int. 2011 Jul 15;210(1-3):206-12. Epub 2011 Apr 6.

Desorption atmospheric pressure photoionization-mass spectrometry in routine analysis of confiscated drugs.

Kauppila TJ, Flink A, Haapala M, Laakkonen UM, Aalberg L, Ketola RA, Kostiaainen R.

Division of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Helsinki, P.O. Box 56, Helsinki 00014, Finland. tiina.kauppila@helsinki.fi

A comprehensive study was made, where desorption atmospheric pressure photoionization (DAPPI) was applied to the direct analysis of confiscated drugs and pharmaceuticals of various forms and matrices. The analyzed samples included herbal products [Catha edulis (khat), Psilocybe mushrooms, opium and Spice], designer drugs in tablet and powder form [e.g. meta-chlorophenylpiperazine (mCPP), 3-fluoromethamphetamine (3-FMA), methylenedioxypropylvalerone (MDPV) and methylone], and anabolic steroids in oil and tablets. The analyses were performed with ion trap mass spectrometer in MS and MS(2) modes and the obtained spectra were compared with GC-MS results. Contamination of the mass spectrometer was avoided by careful adjustment of the distance of the sample from the mass spectrometer inlet. DAPPI proved to be a fast and specific analysis technique, which does not require any sample preparation, and which therefore suits well to this type of forensic analysis.

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PMID: 21474259 [PubMed]

20. Forensic Sci Int. 2011 Jun 15;209(1-3):126-32. Epub 2011 Feb 11.

Spectroscopic characterization of 3,4-methylenedioxypropylvalerone: a new designer drug with α -pyrrolidinophenone structure.

Westphal F, Junge T, Klein B, Fritschi G, Girreser U.

State Bureau of Criminal Investigation Schleswig-Holstein, Section
Narcotics/Toxicology, Kiel, Germany. dr.-folker.westphal@polizei.landsh.de

This study presents and discusses the infrared spectroscopic, the nuclear magnetic resonance spectroscopic and mass spectrometric data of the designer drug 3,4 methylenedioxy-pyrrolidinobutyrophenone (MDPBP), a homolog of 3,4 methylenedioxypropylone (MDPV). MDPBP was first seized in Germany in the year 2009. The structure elucidation of the aliphatic part of MDPBP was carried out by product ion spectrometry of the immonium ion with $m/z=112$ formed after electron ionization, and by one- and two-dimensional (^1H) - and (^{13}C) NMR spectroscopy.

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PMID: 21316166 [PubMed]

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- [Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypropylone.](#)
1. [Methylenedioxypropylone.](#)
Borek HA, Holstege CP.
Ann Emerg Med. 2012 Mar 2. [Epub ahead of print]
PMID:22387085[PubMed - as supplied by publisher]
- [Illicit bath salts: not for bathing.](#)
2. Kyle PB, Iverson RB, Gajagowni RG, Spencer L.
J Miss State Med Assoc. 2011 Dec;52(12):375-7.
PMID:22329114[PubMed - in process]
- [Death Following Recreational Use of Designer Drug "Bath Salts" Containing 3,4-Methylenedioxypropylone \(MDPV\).](#)
3. [Methylenedioxypropylone \(MDPV\).](#)
Murray BL, Murphy CM, Beuhler MC.
J Med Toxicol. 2012 Mar;8(1):69-75.
PMID:22271565[PubMed - in process]
- [Serotonin Syndrome Associated With MDPV Use: A Case Report.](#)
4. Mugele J, Nañagas KA, Tormoehlen LM.
Ann Emerg Med. 2012 Jan 9. [Epub ahead of print]
PMID:22237165[PubMed - as supplied by publisher]
- [\[3,4-methylene-dioxy-propylone \(MDPV\) epidemic?\].](#)
5. Kalapos MP.
Orv Hetil. 2011 Dec 11;152(50):2010-9. Review. Hungarian.
PMID:22112374[PubMed - indexed for MEDLINE]
- [The toxicology of bath salts: a review of synthetic cathinones.](#)
6. Prosser JM, Nelson LS.
J Med Toxicol. 2012 Mar;8(1):33-42.
PMID:22108839[PubMed - in process]
- [Identification of ten new designer drugs by GC-MS, UPLC-QTOF-MS, and NMR as part of a police investigation of a Danish Internet company.](#)
7. [part of a police investigation of a Danish Internet company.](#)
Reitzel LA, Dalsgaard PW, Müller IB, Cornett C.
Drug Test Anal. 2011 Nov 18. doi: 10.1002/dta.358. [Epub ahead of print]
PMID:22102551[PubMed - as supplied by publisher]
- [Energy-1 \('NRG-1'\): don't believe what the newspapers say about it being legal.](#)
8. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, Dargan PI.
Emerg Med J. 2011 Dec;28(12):1068-70.
PMID:22101594[PubMed - indexed for MEDLINE]
- [Schedules of controlled substances: temporary placement of three synthetic cathinones in Schedule I. Final Order.](#)
9. [cathinones in Schedule I. Final Order.](#)
Drug Enforcement Administration, Department of Justice.
Fed Regist. 2011 Oct 21;76(204):65371-5.
PMID:22016903[PubMed - indexed for MEDLINE] **Free Article**

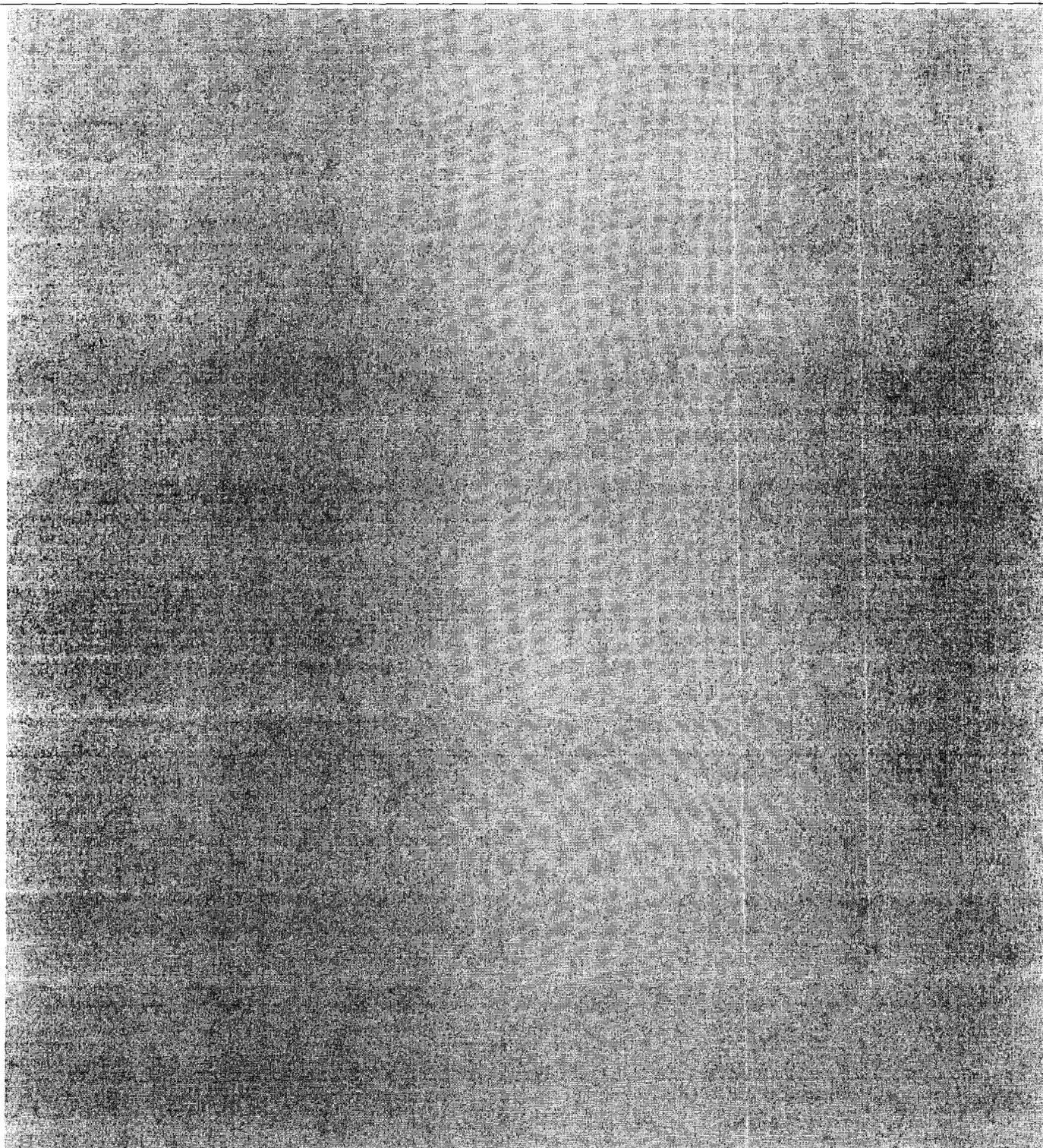
000212

10. 3,4-methylenedioxypropylone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online.
Coppola M, Mondola R.
Toxicol Lett. 2012 Jan 5;208(1):12-5. Epub 2011 Oct 8. Review.
PMID:22008731[PubMed - indexed for MEDLINE]
- Analysis of NRG 'legal highs' in the UK: identification and formation of novel
11. cathinones.
Brandt SD, Freeman S, Sumnall HR, Measham F, Cole J.
Drug Test Anal. 2011 Sep;3(9):569-75. doi: 10.1002/dta.204. Epub 2010 Dec 29.
PMID:21960541[PubMed - indexed for MEDLINE]
- The analysis of substituted cathinones. Part 3. Synthesis and characterisation of 2,3-
12. methylenedioxy substituted cathinones.
Kavanagh P, O'Brien J, Fox J, O'Donnell C, Christie R, Power JD, McDermott SD.
Forensic Sci Int. 2012 Mar 10;216(1-3):19-28. Epub 2011 Sep 9.
PMID:21907509[PubMed - in process]
- Clinical experience with and analytical confirmation of "bath salts" and "legal
13. highs" (synthetic cathinones) in the United States.
Spiller HA, Ryan ML, Weston RG, Jansen J.
Clin Toxicol (Phila). 2011 Jul;49(6):499-505.
PMID:21824061[PubMed - indexed for MEDLINE]
- Hallucinatory delirium following use of MDPV: "Bath Salts".
14. Penders TM, Gestring R.
Gen Hosp Psychiatry. 2011 Sep-Oct;33(5):525-6. Epub 2011 Jul 16. No abstract available.
PMID:21762997[PubMed - indexed for MEDLINE]
- Development of a rapid LC-MS/MS method for direct urinalysis of designer drugs.
15. Bell C, George C, Kicman AT, Traynor A.
Drug Test Anal. 2011 Jul-Aug;3(7-8):496-504. doi: 10.1002/dta.306. Epub 2011 Jul 11.
PMID:21744513[PubMed - indexed for MEDLINE]
- Emergency department visits after use of a drug sold as "bath salts"--Michigan,
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Centers for Disease Control and Prevention (CDC).
MMWR Morb Mortal Wkly Rep. 2011 May 20;60(19):624-7.
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- Identification and characterization of the new designer drug 4'-methylethcathinone (4-
17. MEC) and elaboration of a novel liquid chromatography-tandem mass spectrometry (LC-MS/MS) screening method for seven different methcathinone analogs.
Jankovics P, Váradi A, Tölgyesi L, Lohner S, Németh-Palotás J, Koszegi-Szalai H.
Forensic Sci Int. 2011 Jul 15;210(1-3):213-20. Epub 2011 Apr 16.
PMID:21498012[PubMed]
- New designer drug of abuse: 3,4-Methylenedioxypropylone (MDPV). Findings from
18. apprehended drivers in Finland.
Kriikku P, Wilhelm L, Schwarz O, Rintatalo J.
Forensic Sci Int. 2011 Jul 15;210(1-3):195-200. Epub 2011 Apr 7.
PMID:21477955[PubMed - indexed for MEDLINE]
- Desorption atmospheric pressure photoionization-mass spectrometry in routine
19. analysis of confiscated drugs.
Kauppila TJ, Flink A, Haapala M, Laakkonen UM, Aalberg L, Ketola RA, Kostianen R.

Forensic Sci Int. 2011 Jul 15;210(1-3):206-12. Epub 2011 Apr 6.
PMID:21474259[PubMed]

- Spectroscopic characterization of 3,4-methylenedioxy-pyrrolidinobutyrophenone: a new designer drug with α -pyrrolidinophenone structure.

Westphal F, Junge T, Klein B, Fritschi G, Girreser U.
Forensic Sci Int. 2011 Jun 15;209(1-3):126-32. Epub 2011 Feb 11.
PMID:21316166[PubMed]



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- [Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography-mass spectrometry.](#)
21. Ojanperä IA, Heikman PK, Rasanen IJ.
Ther Drug Monit. 2011 Apr;33(2):257-63.
PMID:21240056[PubMed - indexed for MEDLINE]
- [Analysis of NRG 'legal highs' in the UK: identification and formation of novel cathinones.](#)
22. Brandt SD, Freeman S, Sumnall HR, Measham F, Cole J.
Drug Test Anal. 2010 Dec 29. [Epub ahead of print]
PMID:21191917[PubMed - as supplied by publisher]
- [Studies on the metabolism of the \$\alpha\$ -pyrrolidinophenone designer drug methylenedioxypropylvalerone \(MDPV\) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS.](#)
23. Meyer MR, Du P, Schuster F, Maurer HH.
J Mass Spectrom. 2010 Dec;45(12):1426-42.
PMID:21053377[PubMed - indexed for MEDLINE]
- [Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone \(MDPV\) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry.](#)
24. Strano-Rossi S, Cadwallader AB, de la Torre X, Botrè F.
Rapid Commun Mass Spectrom. 2010 Sep;24(18):2706-14.
PMID:20814976[PubMed - indexed for MEDLINE]
- [Analyses of second-generation 'legal highs' in the UK: initial findings.](#)
25. Brandt SD, Sumnall HR, Measham F, Cole J.
Drug Test Anal. 2010 Aug;2(8):377-82.
PMID:20687197[PubMed - indexed for MEDLINE]
- [Molecular detection of Muscovy duck parvovirus by loop-mediated isothermal amplification assay.](#)
26. Ji J, Xie QM, Chen CY, Bai SW, Zou LS, Zuo KJ, Cao YC, Xue CY, Ma JY, Bi YZ.
Poult Sci. 2010 Mar;89(3):477-83.
PMID:20181863[PubMed - indexed for MEDLINE] **Free Article**
- [Genetic variance of Derzsy's disease strains isolated in Poland.](#)
27. Woźniakowski G, Kozdrun W, Samorek-Salamonowicz E.
J Mol Genet Med. 2009 Nov 30;3(2):210-6.
PMID:20076793[PubMed] **Free PMC Article**
- [Development and evaluation of a VP3-ELISA for the detection of goose and Muscovy duck parvovirus antibodies.](#)
28. Zhang Y, Li Y, Liu M, Zhang D, Guo D, Liu C, Zhi H, Wang X, Li G, Li N, Liu S, Xiang W, Tong G.
J Virol Methods. 2010 Feb;163(2):405-9. Epub 2009 Nov 11.
PMID:19913055[PubMed - indexed for MEDLINE]

- Mass and NMR spectroscopic characterization of 3,4-methylenedioxypropylvalerone: a designer drug with alpha-pyrrolidinophenone structure.
29. Westphal F, Junge T, Rösner P, Sönnichsen F, Schuster F.
Forensic Sci Int. 2009 Sep 10;190(1-3):1-8. Epub 2009 Jun 4.
PMID:19500924[PubMed]
- [Analysis of designer drugs detected in the products purchased in fiscal year 2006].
30. Uchiyama N, Kikura-Hanajiri R, Kawahara N, Goda Y.
Yakugaku Zasshi. 2008 Oct;128(10):1499-505. Japanese.
PMID:18827471[PubMed - indexed for MEDLINE] **Free Article**
- Ginkgo biloba extract improves coronary artery circulation in patients with coronary artery disease: contribution of plasma nitric oxide and endothelin-1.
31. Wu YZ, Li SQ, Zu XG, Du J, Wang FF.
Phytother Res. 2008 Jun;22(6):734-9.
PMID:18446847[PubMed - indexed for MEDLINE]
- Ginkgo biloba extract improves coronary blood flow in healthy elderly adults: role of endothelium-dependent vasodilation.
32. Wu Y, Li S, Cui W, Zu X, Du J, Wang F.
Phytomedicine. 2008 Mar;15(3):164-9. Epub 2008 Feb 6.
PMID:18258419[PubMed - indexed for MEDLINE]
- Ginkgo biloba extract improves coronary blood flow in patients with coronary artery disease: role of endothelium-dependent vasodilation.
33. Wu Y, Li S, Cui W, Zu X, Wang F, Du J.
Planta Med. 2007 Jun;73(7):624-8. Epub 2007 Jun 13.
PMID:17564952[PubMed - indexed for MEDLINE]
- Isolation and molecular characterization of a new Muscovy duck parvovirus from Muscovy ducks in the USA.
34. Poonia B, Dunn PA, Lu H, Jarosinski KW, Schat KA.
Avian Pathol. 2006 Dec;35(6):435-41.
PMID:17121731[PubMed - indexed for MEDLINE]
- Expression of capsid proteins and non-structural proteins of waterfowl parvoviruses in Escherichia coli and their use in serological assays.
35. Wang CY, Shieh HK, Shien JH, Ko CY, Chang PC.
Avian Pathol. 2005 Oct;34(5):376-82.
PMID:16236567[PubMed - indexed for MEDLINE]
- Genetic variation of viral protein 1 genes of field strains of waterfowl parvoviruses and their attenuated derivatives.
36. Tsai HJ, Tseng CH, Chang PC, Mei K, Wang SC.
Avian Dis. 2004 Sep;48(3):512-21.
PMID:15529973[PubMed - indexed for MEDLINE]
- Evidence of Muscovy duck parvovirus in Muscovy ducklings in California.
37. Woolcock PR, Jestin V, Shivaprasad HL, Zwingelstein F, Arnauld C, McFarland MD, Pedersen JC, Senne DA.
Vet Rec. 2000 Jan 15;146(3):68-72.
PMID:10674693[PubMed - indexed for MEDLINE]
- Phylogenetic analysis of parvoviruses isolated in Taiwan from ducks and geese.
38. Chang PC, Shien JH, Wang MS, Shieh HK.
Avian Pathol. 2000 Feb;29(1):45-9.

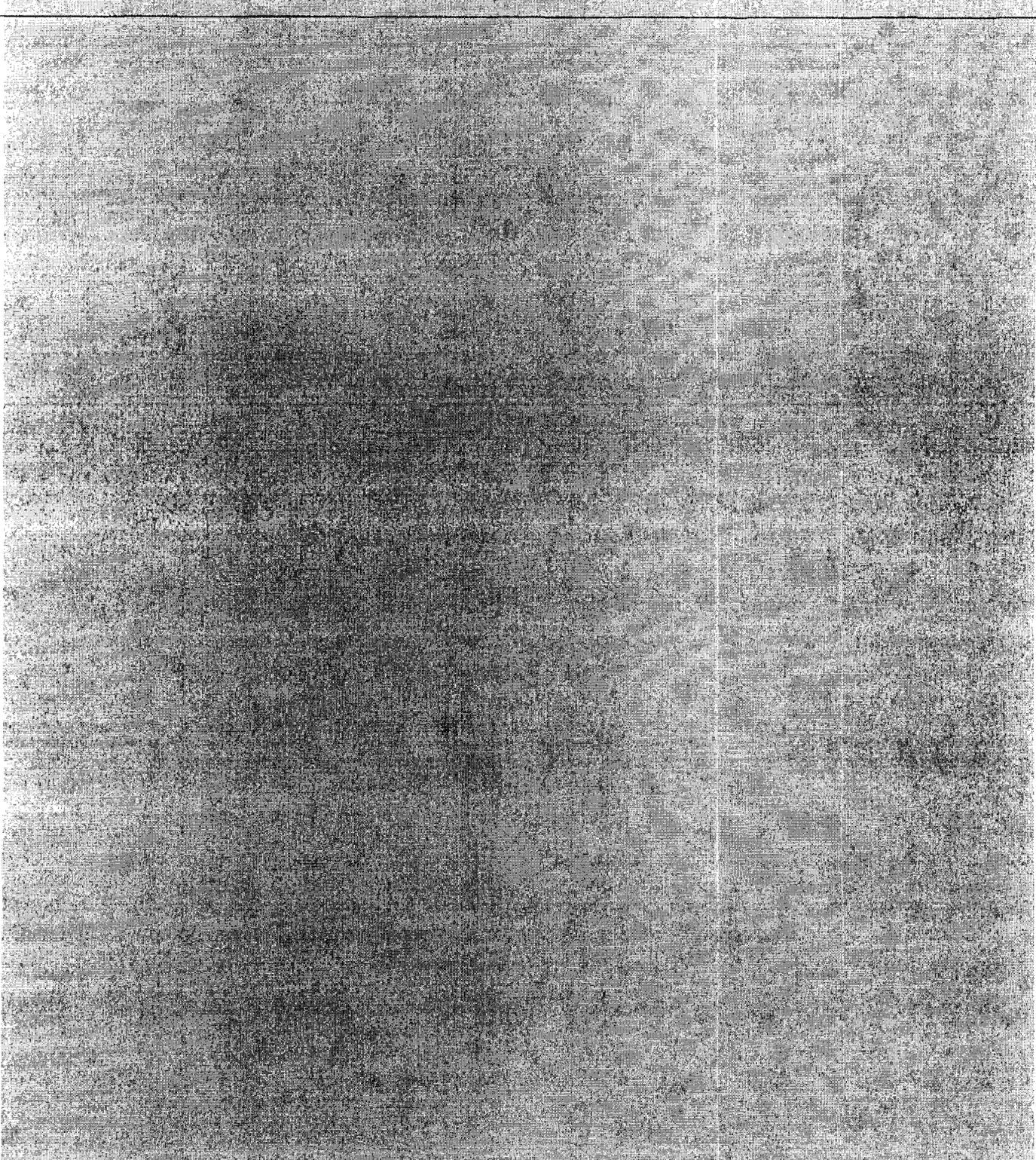
PMID:19184788[PubMed - in process]

- Γ Detection of goose and Muscovy duck parvoviruses using polymerase chain reaction-
- 39. restriction enzyme fragment length polymorphism analysis.

Sirivan P, Obayashi M, Nakamura M, Tantaswasdi U, Takehara K.

Avian Dis. 1998 Jan-Mar;42(1):133-9.

PMID:9533090[PubMed - indexed for MEDLINE]



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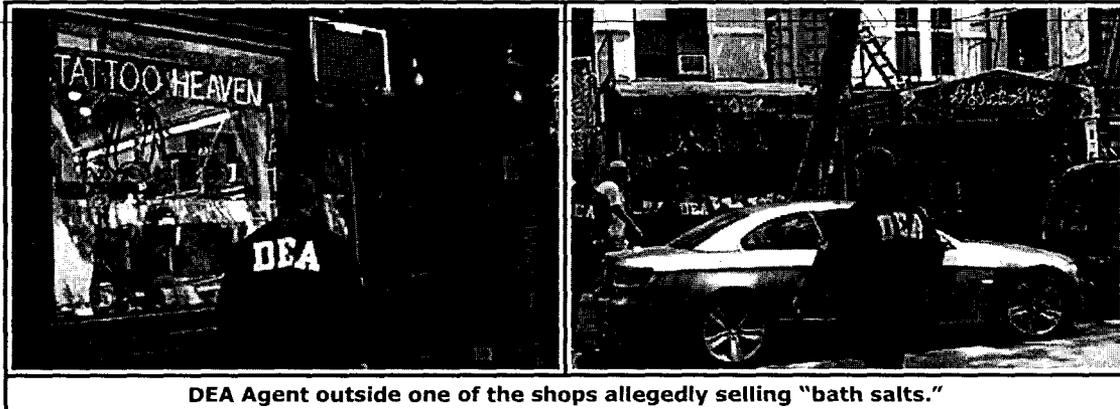
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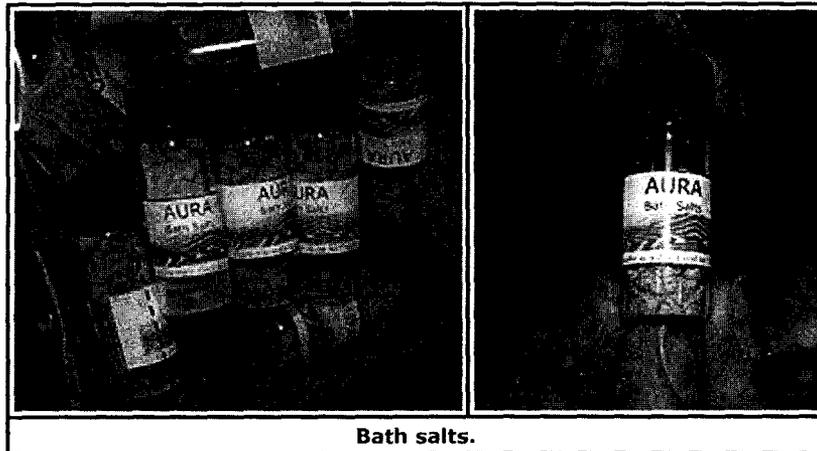
Ten Arrested in New York "Bath Salts" Round-Up



DEA Agent outside one of the shops allegedly selling "bath salts."

JUN 28 -- MANHATTAN - John Gilbride, the Special Agent in Charge of the New York Division of the Drug Enforcement Administration (DEA) and Preet Bharara, the United States Attorney for the Southern District of New York, announced the arrest against a major distributor of "bath salts," a recreational designer drug with significant and dangerous adverse effects. Nine employees of retail shops in Manhattan and Brooklyn that sold the drug were also arrested. Charged today are the distributor, Miguel Ashby, and Sellers Maxim Amar, Diana Asaro, Nassar Atrach, Yakob Biton, Dimitry Farber, Sufiyan Ganchi, Gabrielle Grife, Igor Kanchik, and Steve Zhik.

"Nationwide the abuse of 'bath salts' has led to serious health consequences and death. This investigation is further evidence that DEA and our law enforcement partners will not sit by while a new form of drug abuse takes hold," said Gilbride. "Let this be a message to not only those who sell this poison, but to those who abuse 'bath salts' that this road leads to a dead end."



Bath salts.

"Bath salts are one of the latest designer drugs to reach our shores, and they have proven to be a public health and safety menace with serious, and sometimes deadly, consequences," said Bharara. "The investigation that culminated in today's arrests should demonstrate the seriousness with which we and our law enforcement partners at the DEA take the threat posed by this drug, and the consequences for those who would distribute and sell it."

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According to the complaint unsealed today in Manhattan federal court today: Since February 2011, the DEA's New York Field Division has been investigating the importation, distribution, and use of "bath salts," which are synthetic stimulants that have no real value as a bath salt or other bath product. Their only known purpose is to be consumed as a recreational drug. "Bath salts" first emerged in the United States approximately two years ago. The drug is typically snorted in powder form or ingested in pill form, but it can also be smoked or injected intravenously. While its effects may vary, users typically experience highs similar to that of the drug Ecstasy, and stimulants like cocaine and methamphetamines. Adverse effects include psychotic episodes, delusions, panic attacks, and increased heart rate. The abuse of "bath salts" has been linked to death, suicide, homicide, self-inflicted wounds, and child endangerment. Companies located in China and India are principally responsible for manufacturing and exporting the drug. Shippers typically mislabel the product to evade detection by law enforcement, and sell it via the Internet to distributors around the world, including in the United States. U.S. distributors then sell the drug online, through traditional distribution methods, or by retail distribution at convenience stores, gas stations, and head shops (retail stores specializing in drug paraphernalia).

"Bath salts" are also often sold in dance clubs and at underground parties known as "raves". They typically sell for approximately \$40 to \$100 per gram, and each packet contains approximately one quarter to one gram. A gram consists of approximately eight to 40 doses.

Packets of "bath salts" are branded with names such as "Aura," "Ivory Wave," "Russian River," "Xtreme," "Goodfellas," and other. They are often labeled "not for human consumption" in an effort to circumvent federal narcotics laws. Despite these warnings, sellers market "bath salts" as recreational drugs.

In February 2011, the DEA Field Office in New York established a Bath Salts Task Force ("BSTF") to investigate sellers of the drug in the greater New York City area. From February to June 2011, the BSTF investigated a number of different head shops and stores that reportedly sold "bath salts," including those where the nine defendants worked. They are all located in Manhattan, with the exception of one, which is located in Brooklyn, New York. The investigation revealed that ASHBY supplied "bath salts" to the stores that employed Farber, Kanchik, Grife, and Zhik. The investigation also found that Amar, Asaro, Atrach,

Biton, Ganchi, Farber, Grife, Kanchik, and Zhik sold the drug out of the head shops where they each worked. Using undercover agents, which were recorded by the DEA, the BSTF purchased over a kilogram of "bath salts" in total from the stores. During the undercover buys, certain of the defendants discussed how to ingest the "bath salts," and one boasted that the use of "bath salts" would not appear in a urinalysis. The BSTF seized approximately 40 kilograms of the drug during the course of the investigation, valued at approximately \$2 million on the street.

Subsequent to the New York State Health Commissioner's May 23, 2011, ban on the sale and distribution of "bath salts," several of the defendants employed at the head shops represented that they continued to have the drug available for sale, and one defendant represented that he could obtain additional "bath salts" to sell.

The defendants were arrested this morning and will be presented in Magistrate Court later today. A chart setting forth the charges in the Complaint and the applicable penalties is attached. Mr. Bharara praised the investigative work of the DEA New York Field Office.

The prosecution is being handled by the Office's Narcotics Unit. Assistant U.S. Attorneys Santosh Aravind and Timothy Sini are in charge of the prosecution.



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News from DEA, News Releases, 10/21/11
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DEA, News Releases, 2011
 ... Month Investigation. OCT 21, 2011, Chemicals Used in "Bath Salts"
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[PDF] March 2004 Microgram Bulletin
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... Numerous retail products marketed under the guise of "**bath salts**" and "plant food" have been analyzed and mephedrone, methylone, and MDPV ...
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DEA Major Arrests News Releases
... Dollar Drug-Trafficking Conspiracy. JUN 28, 2011, Ten Arrested in New York "**Bath Salts**" Round-Up. JUN 21, 2011, Three ...
www.justice.gov/dea/pubs/pressrel/majorarrests_archives2011.html-28k- Cached

News from DEA, Domestic Field Divisions, New York City ...
... First New York Rx Summit. JUN 28, 2011, Ten Arrested in New York "**Bath Salts**" Round-Up. JUN 21, 2011, Three FARC Guerillas ...
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[PDF] – SCHEDULING UPDATE – - NOVEMBER 2011 -
... Mephedrone, methylone, and MDPV are falsely marketed as "research chemicals," "plant food," or "**bath salts**." They are sold at smoke shops, head ...
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... Over the past few months, there has been a growing use of, and interest in, synthetic stimulants sold under the guise of "**bath salts**" or "plant food". ...
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New designer drug of abuse: 3,4-Methylenedioxypropylvalerone (MDPV). Findings from apprehended drivers in Finland

Pirkko Kriikku^{a,*}, Lars Wilhelm^b, Olaf Schwarz^b, Janne Rintatalo^c

^aVita Health Care Services Ltd., Vita Laboratory, Laivakatu 5 F, 00150 Helsinki, Finland

^bLADR GmbH Medizinisches Versorgungszentrum Dr. Kramer und Kollegen, Lauenburger Straße 67, 21502 Geesthacht, Germany

^cNational Bureau of Investigation Forensic Laboratory, Jokiniemenkuja 4, 01370 Vantaa, Finland

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ABSTRACT

Starting in 2008 a new designer drug, 3,4-methylenedioxypropylvalerone (MDPV) appeared among users of illegal drugs in Finland. Since then there have been several seizures of MDPV by police and customs and it has been connected to many crimes of different types. In this study the incidence and impact of the use of MDPV in drivers suspected of being under the influence of drugs (DUID) in Finland was assessed.

Since autumn 2009, blood samples from drivers suspected of DUID in Finland have been analysed for the presence of MDPV. A new LC-MS/MS method for the determination of MDPV in serum was established. In order to assess the impact of MDPV on driving performance, drug and alcohol findings of positive MDPV cases were compared with data from the clinical examination carried out while the suspect was under arrest. In a period of one year there were 259 positive MDPV cases from apprehended drivers (5.7% of all confirmed DUID cases). In 80% of the cases in which MDPV was found, amphetamine was also present. Benzodiazepines were also frequently found together with MDPV, which was to be expected since in Finland, in our experience, stimulants are very often used together with benzodiazepines.

In most cases it remained unclear whether the observed psycho-physical achievement deficiency was induced by MDPV because the concentrations of other drugs, especially other stimulants, were often high. However, in some subjects, MDPV, or MDPV in combination with other substances was the most probable cause of the impairment. The concentrations of MDPV varied from 0.016 mg/L to over 8.000 mg/L.

Little is known about the pharmacology of MDPV. However, based on our findings it is clear that MDPV has a serious impact on traffic safety in Finland.

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1. Introduction

MDPV (Fig. 1) is a so-called “designer drug” with stimulant effects similar to cocaine and amphetamine. It is an analogue of propylvalerone, a psychostimulant that was used to treat lethargy and chronic fatigue in the 1970s, but was later withdrawn from the market because of problems with abuse and dependency [1,2]. MDPV structurally resembles cathinone, found in Khat, and has thus been referred to as a synthetic cathinone derivative [3].

MDPV has no medical use and is said to have exceptionally high dependency potential and high risk of psychosis. At higher doses some users report extremely unpleasant “come-down” effects [4]. Police reports indicate that people under the influence of MDPV

very often act violently and unpredictably. MDPV is most often sold as powder, but capsules have also been reported. A wide range of dosage forms and routes of administration are used: oral (capsules or powder dissolved in water), IV, rectal [4].

Very recently, Ojanperä et al. published their results about MDPV findings from the urine of opioid-dependent patients [5], which is, other than our results, the only published study about MDPV in clinical samples. There are, however, some data on the pharmacology and toxicology of other structurally similar designer drugs of pyrrolidinophenone or cathinone types available [6–9]. Also some reports on the structure and determination and *in vitro* metabolism of MDPV have been published recently [10–13].

Since the first seizure of MDPV in Finland in 2008, there have been several deaths where involvement of MDPV was suspected by the police (personal communication). Whether the actual cause of these deaths really was MDPV or perhaps some other drug used in combination with it is still not settled. It seems that MDPV is a major phenomenon only in Finland. There have been some reports

* Corresponding author. Tel.: +358 9 2288 0480; fax: +358 9 2288 0413.

E-mail addresses: pirkko.kriikku@vita.fi, pirkko.kriikku@helsinki.fi (P. Kriikku), wilhelm@ladr.de (L. Wilhelm), janne.rintatalo@poliisi.fi (J. Rintatalo).

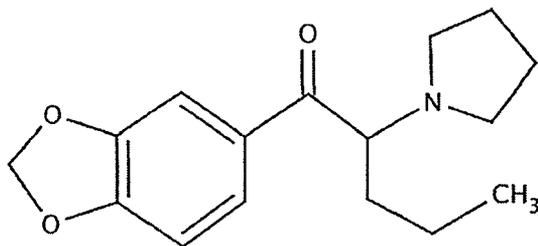


Fig. 1. 1-(3,4-Methylenedioxyphenyl)-2-pyrrolidinylpentan-1-one (methylenedioxypropylvalerone, MDPV).

of cases also in other countries (United Kingdom, Ireland and Sweden) but not on the scale seen in Finland [14–16].

In our laboratory, screening of MDPV was initiated at the request of the Forensic Laboratory of the Finnish National Bureau of Investigation (NBI), after there had been several seizures of MDPV by police. The drug screening procedures currently used by the police in Finland (e.g. DrugWipe, Securetec/Afiniton, Williamsport, PA, USA), fail to detect MDPV, as is true for most other designer drugs. Since August 2009 blood samples from drivers suspected of being under the influence of drugs (DUID) have been analysed for the presence of MDPV. Initially, a qualitative screening method using LC–MS/MS was developed. After a commercial reference standard came available, it became possible to convert this assay into the quantitative confirmation method for the determination of MDPV described in this paper.

In many DUID cases in Finland the suspect is given a psycho-physical achievement test by a physician after the arrest. The requirement for the test is determined by the severity of the suspected crime. The test includes specific psychomotor and cognitive tasks and questions. Based on the results of the tests the physician describes the overall functional impairment of the subject using a three-step scale: within the normal range, mild aberrations, moderate or greater aberrations. Although such tests provide evidence of drug effects on the arrested driver, they do not specifically demonstrate driving impairment [17]. Furthermore, due to the possible impact of acute and chronic tolerance, blood concentrations do not necessarily reflect the degree of impairment observed in the psycho-physical achievement test. These issues lead to difficulty in establishing guidelines for the concentrations of drugs that are dangerous or impair driving. In Finland, the authorities do not need to prove actual driving impairment when a suspect of DUID is taken into custody; a suspicion of DUID is a sufficient reason for the arrest. The psycho-physical achievement deficiency test provides additional information that can be used in setting penalties: higher penalties in cases with aberrations.

The aim of this study was to report on the prevalence and significance of MDPV among drivers apprehended for DUID in Finland. In MDPV positive cases, drug and alcohol findings were compared with data from the clinical examination carried out while the suspect was under arrest. The psycho-physical achievement deficiency information was used to evaluate the significance of the presence of MDPV in DUID cases. We also report concentrations of MDPV in the blood of DUID offenders.

2. Materials and methods

2.1. Chemicals and reagents

The reference standard of MDPV (purity 98%) used for the quantitative determination and the (\pm)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5) used as internal standard were obtained from LGC Standards (Wesel, Germany). For the qualitative analysis that was used before the availability of a reference standard made a quantitative assay possible, a seized MDPV sample (VARA-4108, purity 4%) supplied by NBI Forensic Laboratory, Vantaa, Finland was used to develop the assay and check reproducibility. HPLC grade methanol, water, ammonia 32% p.a. and acetic acid p.a.

were purchased from Baker (Griesheim, Germany) and formic acid 98–100% from Merck (Darmstadt, Germany). As the solid phase column an OASIS HLB 1 cc 30 mg from Waters (Eschborn, Germany) was used.

2.2. Sample preparation

The first step of sample preparation consisted of adding 0.8 mL 0.1 M acetic acid and 20 μ L of an internal standard solution to 0.2 mL of test material (serum or control). The internal standard solution contained 500 ng/mL MDEA-d5 in methanol. Spiked samples were vortex mixed for 10 s and centrifuged at 13 000 rpm for 3 min.

Sample cleanup was performed by solid phase extraction (SPE) using OASIS HLB cartridges with 30 mg sorbent. The SPE cartridges were conditioned with 1 mL of methanol and 1 mL of deionised water. Supernatants were loaded on the cartridges and drawn through under gravity flow. The cartridges were washed with 1 mL of a mixture of deionised water, methanol and ammonia (93:5:2, v/v/v) and 1 mL of a mixture of deionised water, methanol and ammonia (78:20:2, v/v/v). The cartridges were dried for 10 min in order to remove washing solutions. The analytes were then desorbed with 1 mL methanol and acetic acid (95:5, v/v). The eluted solutions were evaporated under a nitrogen stream at 45 °C, and the residue was reconstituted with 0.5 mL of a mixture of methanol and 10 mM NH_4 acetate in 0.1% formic acid (80:20, v/v). After vortex mixing, 5 μ L sample was injected into the LC–MS/MS system.

2.3. LC–MS/MS conditions

The LC–MS/MS system consisted of a Shimadzu LC 20A LC-system and a triple quadrupole mass spectrometer (API 4000, SCIEX) with Turbo Ion Spray. Chromatography with a total runtime of 5.5 min was performed using a phenyl-hexyl 50 mm \times 3.0 mm 3 μ m column from Phenomenex operated in gradient mode at 0.5 mL/min. Solvent A consisted of methanol and Solvent B of 10 mM NH_4 acetate in 0.1% formic acid. The column oven temperature was set to 40 °C. Multiple reaction monitoring (MRM) was created for the analyte and internal standard (MDPV m/z 276/126 and m/z 276/135, MDEA-d5 m/z 213/163) in positive ion mode at the ionisation voltage of 4200 V, the source temperature being 550 °C.

Integration of peak areas and standard calibration for the MRM transitions were performed using the quantification tool of Analyst 1.5.1 software (SCIEX). Confirmatory analysis was performed based on the ratio of two MRM transitions detected for each analyte.

The validation of the method was performed according to the guidelines of the GTFCh (Gesellschaft für Toxikologie und Forensische Chemie) for limit of detection, limit of quantification, precision, recovery, selectivity and matrix effect [18]. No interference was found with any of the 38 most commonly occurring stimulants, sedatives and opioids that were analysed together with MDPV. The procedure also included verification of isobar mass transitions from the literature [19,20]. The calculations for the limit of detection were performed according to the German standard specification DIN 32645 [21].

The limit of detection (LOD) for MDPV was 0.003 mg/L and the limit of quantification 0.011 mg/L. The calibration was linear over the range 0.010–0.500 mg/L. For sample concentrations exceeding the calibration range the curve was extended and an approximate value was given as a result. The extraction recovery was determined at the lowest and highest point of the calibration in blank serum, and was found to be 67.9% at 0.200 mg/L and 89.8% at 0.020 mg/L. The matrix effect, measured in 6 different samples, was 21.5%. Precision was measured at two different concentrations, 0.015 mg/L and 0.400 mg/L, by performing two analyses on 8 different days. The standard deviation (CV) of within- and between-day repeatability was between 9.5% and 11.8%. Accuracy ranged between 3.9% and 5.2%.

LC–MS/MS chromatograms of a blank, a spiked sample and a real sample are presented in Figs. 2–4.

3. Results and discussion

Prior to development of the quantitative assay, the screening assay was used to determine whether samples were positive or negative for the presence of MDPV, i.e., above or below the limit of detection for MDPV, 0.003 mg/L. After the quantitative assay became available, samples were initially screened using the non-quantitative assay and for those found to be positive the quantitative assay was performed using a separate aliquot of serum.

In Finland, the number of cases per year of driving under the influence of drugs or alcohol in which a blood sample is taken is over 12 500. In approximately 4570 of them a drug analysis was requested. MDPV is, however, not screened from every sample. Between 28 August 2009 and the end of August 2010, blood

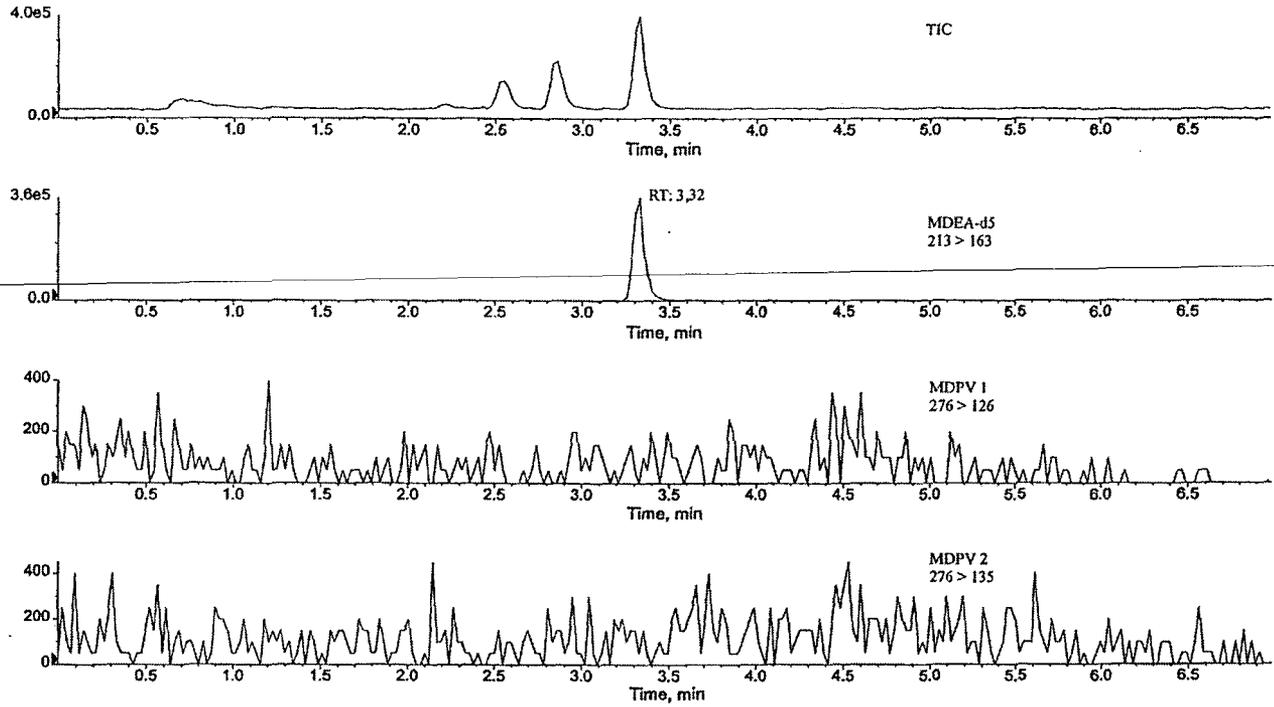


Fig. 2. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a blank sample with 0.050 mg/L of internal standard (\pm)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

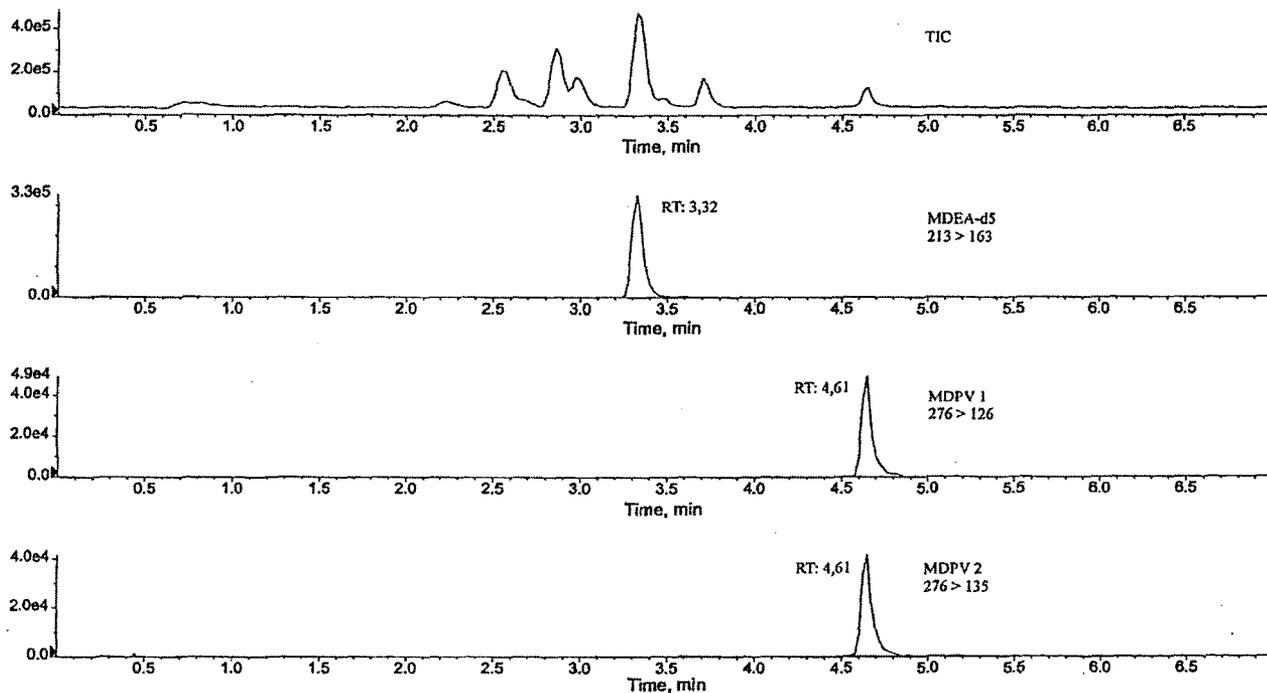


Fig. 3. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a blank sample spiked with a concentration of 0.015 mg/L of methylenedioxypropylvalerone (MDPV) and with 0.050 mg/L of internal standard (\pm)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

samples from about 3000 drivers apprehended on suspicion of DUI were analysed for the presence of MDPV. These cases were not selected randomly and are not necessarily representative of the overall DUI population. They were selected partly on the basis of the needs of and information provided by the police, e.g., drivers admitted use of MDPV or amphetamine-like drugs, failure to detect other drugs which could explain aberrant behaviour. A positive

immunological blood screening test for amphetamines was also an indication for an MDPV analysis, even though MDPV does not show in that test.

Of the samples screened for MDPV in this one year period, 259 (8.6%, $n = 3000$) were found to be positive. This represents approximately 5.7% of all confirmed DUI cases excluding alcohol-only cases ($n = 4570$) in Finland over the same time

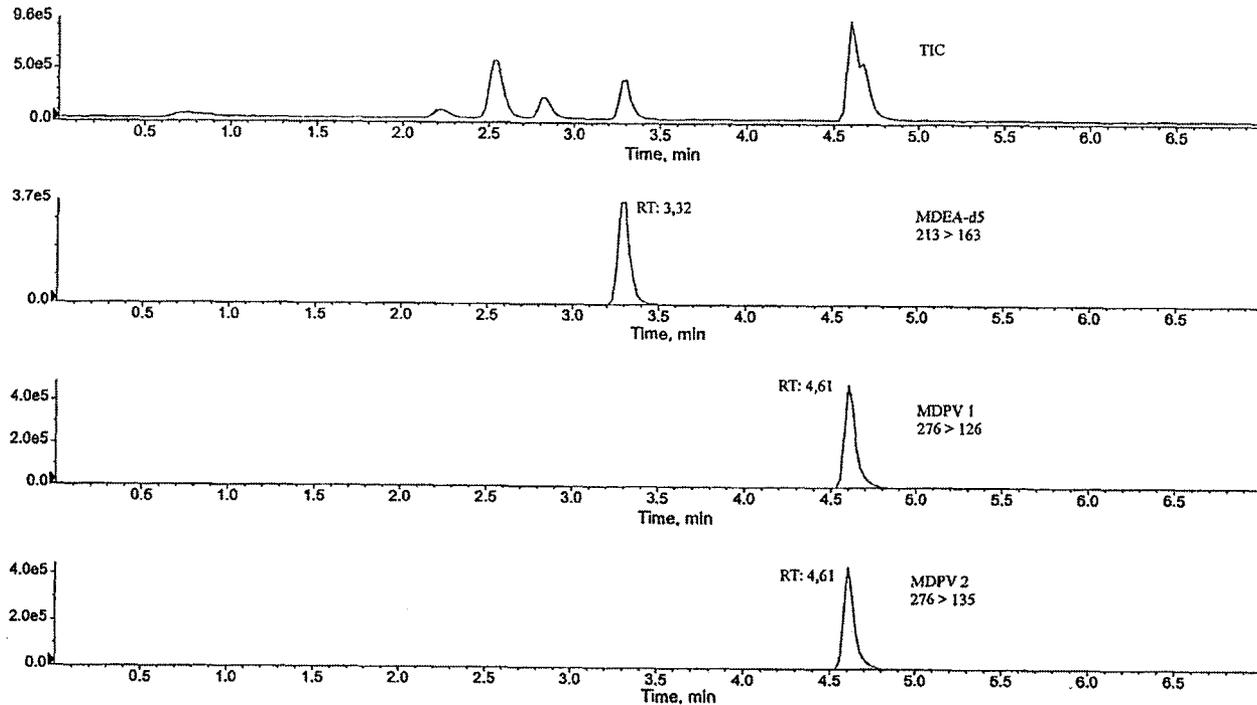


Fig. 4. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a representative positive sample from an apprehended driver containing 0.164 mg/L of methylenedioxypropylamphetamine (MDPV) and 0.050 mg/L of internal standard (\pm)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

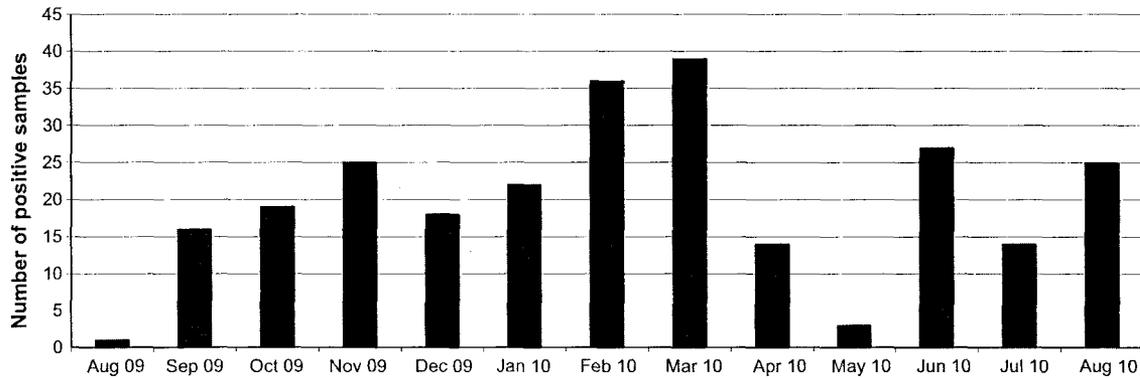


Fig. 5. The numbers of positive methylenedioxypropylamphetamine (MDPV) samples among apprehended drivers in Finland between 28 August 2009 and the end of August 2010.

period. The monthly numbers of positive MDPV samples between August 2009 and August 2010 are illustrated in Fig. 5. 87% of the MDPV positive drivers were male, 96% were from Southern Finland and 76% were between 25 and 44 years.

Of all the 259 MDPV positive cases, in 80% amphetamine and in 67% benzodiazepines were also present. A combination of MDPV, amphetamine and benzodiazepines was found in 54% of the cases. Interestingly, MDPV was often found together with phenazepam, which is a widely abused benzodiazepine that has not been approved for prescription use in Finland. Alcohol was present in only 22 cases (8.5%) and in 18 of them was below the level (0.5 g/L) that defines intoxication in Finland. Surprisingly, the levels of benzodiazepines and most other drugs were often low compared to levels associated with major behaviour effects. However, the levels of other stimulants found together with MDPV were in most cases high. The high percentage of multi-drug findings among the positive MDPV samples is generally typical of DUID cases in Finland [22]. In 8 cases were no other compounds besides MDPV found.

The concentrations of MDPV in samples from a typical month, August 2010, are shown in Fig. 6. The concentration range is very

similar to the range of amphetamine concentrations that we see in the DUID samples in Finland. There were two remarkable outliers (2.4 mg/L and 8.4 mg/L) in these samples. Unfortunately, no data

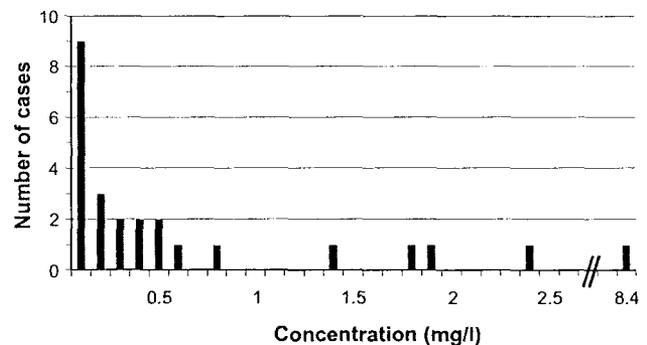


Fig. 6. Concentrations of methylenedioxypropylamphetamine (MDPV) found in the 25 blood samples from apprehended drivers selected for analysis in August 2010.

Table 1
Concentrations of methylenedioxypyrovalerone (MDPV) and other drugs in positive samples from August 2010.

Sample	MDPV (mg/L)	Benzodiazepines ^a	Stimulants ^b	Cannabis ^c	Other findings	Clinical examination
1-08/2010	0.430	±	++		Ethanol	Normal
2-08/2010	1.700	±	++			Aberrations monitored, no overall functional disorder
3-08/2010	1.310	+	++			Aberrations and functional disorder monitored
4-08/2010	2.400					
5-08/2010	0.049	±	++			Aberrations monitored, no overall functional disorder
6-08/2010	0.330	++	++		Methadone	Aberrations and functional disorder monitored
7-08/2010	0.020		++	+		Aberrations and functional disorder monitored
8-08/2010	0.142		+			
9-08/2010	0.020	±	++			
10-08/2010	0.860	±	++	±		Normal
11-08/2010	0.270	+	+		Methadone	Aberrations monitored, no overall functional disorder
12-08/2010	0.050		++			
13-08/2010	0.031	+	++		Zolpidem	
14-08/2010	0.020	±	+		Buprenorphine, tramadol	Aberrations monitored, no overall functional disorder
15-08/2010	0.090		++		Methylphenidate	
16-08/2010	0.380	±	+			Aberrations and functional disorder monitored
17-08/2010	0.550	+	+			
18-08/2010	8.400		++		Methadone	
19-08/2010	0.120	+	++			Aberrations monitored, no overall functional disorder
20-08/2010	0.450	+	++			Aberrations monitored, no overall functional disorder
21-08/2010	0.240	+	++	±		Aberrations and functional disorder monitored
22-08/2010	0.044		++			Normal
23-08/2010	0.044	+	++			
24-08/2010	1.900	±	+			Normal
25-08/2010	0.110		+	+		

- ^a ±One or more benzodiazepines with insignificant concentrations.
+One or more benzodiazepines at concentrations up to those seen at prescribed doses.
++One or more benzodiazepines with concentration above those seen at prescribed doses.
- ^b +Amphetamine, methamphetamine or MDMA concentration <0.100 mg/L.
++Amphetamine, methamphetamine or MDMA concentration ≥0.100 mg/L.
- ^c ±No THC, but THC-COOH positive.
+THC positive.

either on history of drug use or clinical examinations are available in these two cases.

The psycho-physical achievement deficiency test was performed on 208 MDPV positive cases. Functional impairment was found in 84% of these 208 cases but in only 7% was the impairment rated as moderate or greater. Typically the observed aberrations included difficulty in defining the current time, walking in a straight line, turning around and speech. As already mentioned, this evaluation does not demonstrate driving impairment directly, but does give some insight into the impact the drugs had on the subject at the time of the examination. In particular, the impaired judgement and increased willingness to take risks that are associated with the use of stimulants do not necessarily show in the clinical examination.

A summary of the levels of MDPV and other drugs and findings in the clinical tests of the 25 positive samples from August 2010 is illustrated in Table 1. In most MDPV positive cases there was also a considerable amount of amphetamine present in the blood of the suspect. However, there have been some cases where there was reason to believe that the impairment was mainly caused by MDPV. Overall, in 60 of the 259 MDPV positive cases, the analyses showed no other substances, or, the substances found were not at levels sufficient to explain the driving impairment that lead to the arrest. In most of such cases no clinical examination was performed. We introduce one case as an example, where the clinical examination was indeed performed and the concentrations of other drugs beside MDPV were relatively low (case 16-08/2010 in Table 1). The samples of this case were received from the police in Helsinki in the middle of August 2010. The suspected DUID offender was a 28-year old male who had been driving a van at night and had been reported to the police by a citizen. The reason for the report is not known. A roadside drug test was performed on the suspect and it showed positive results for benzodiazepines and amphetamines. The suspect showed aberrations in the clinical

examination, including: unstable gait, balance problems in Romberg's test, his thinking was not clear, depressed and apathetic mood and pupil reaction to light was delayed. In the opinion of the examining physician, the suspect also attempted to disguise his impairment in order to give a misleading impression of normal functioning. The overall functional impairment was, however, estimated to be moderate. The drug analysis of the suspect's blood showed 0.380 mg/L MDPV, low concentrations of benzodiazepines (alprazolam 0.002 mg/L, nordiazepam 0.020 mg/L and oxazepam 0.094 mg/L) and relatively low concentrations of other stimulants (amphetamine 0.092 mg/L and methamphetamine 0.023 mg/L). These other findings were considered to be insignificant in respect to the suspected driving impairment.

There were 219 seizures of MDPV by Finnish Police between 1 January and 31 June 2010 (Fig. 7), accounting for about 45% of all designer drug seizures. Samples of the seized materials were analysed in NBI Forensic Laboratory, Vantaa, Finland. Some samples were found to contain MDPV alone but others contained various mixtures which combined MDPV with benzodiazepines (especially phenazepam) and with other stimulants (especially amphetamine). MDPV confiscated by the Finnish customs has been of Chinese origin.

In the view of the fact that in the past 10 years over 100 new psychotropic substances have appeared on the illicit drug market all over the world, the incidence of MDPV among drivers in Finland is exceptional [23]. MDPV was first reported as new psychoactive substance to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol in 2009 [24]. In Finland MDPV was classified as an illegal drug in June 2010. It has been shown that law enforcement is not a particularly effective deterrent and does not necessarily decrease the prevalence of a particular drug among drivers [25]. However, prior to June 2010 MDPV distributors had the advantage that the drug was not illegal. Presumably, its new designation as an illegal drug will make it less

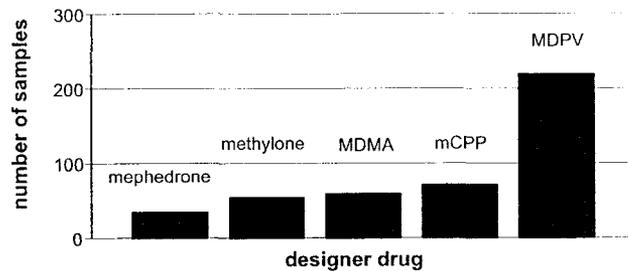


Fig. 7. Most abundant designer drugs seized in Finland between 1 January and 31 August 2010 and analysed by the Finnish National Bureau of Investigation Forensic Laboratory, Vantaa, Finland.

attractive to distributors and result in reduced availability of MDPV.

4. Conclusions

Given the non-random sample selection process and the fact that clinical evaluation and quantitative MDPV data was only available for a sub-set of the samples, the results must be interpreted with particular caution. Nevertheless, it can be concluded that the incidence of MDPV in confirmed DUID cases (excluding alcohol-only cases) is at least 5.7% and could be higher. This is a remarkable number considering that MDPV is a relatively new substance that has only been in Finland for about 2 years. The preponderance of males among MDPV positive cases is typical of all kinds of DUID cases and the 25–44 age range is typical of non-alcohol DUID cases, in our experience. The very high percentage of MDPV positive cases from Southern Finland is somewhat unusual and may reflect a limited distribution of the drug in Finland at this time. The data strongly suggest that MDPV is responsible for at least a portion of the behavioural abnormalities and driving difficulties observed. Since MDPV is most often found together with other psychoactive drugs, it is difficult to determine whether the observed driving impairment was indeed caused by MDPV exclusively, or rather by the combined effect of several substances. However, the results of this study show that MDPV use is a significant problem in DUID cases in Finland. Since at this point it has only been a few months since the legislative change in respect to MDPV, more time is needed to determine whether a decline in the incidence of the drug among Finnish drivers will be achieved. In addition, further studies are needed in order to gain more information on the pharmacology and toxicology of MDPV and to be able to determine what concentrations are dangerous.

Acknowledgements

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References

- [1] G. Gardos, J.O. Cole, Evaluation of pyrovalerone in chronically fatigued volunteers, *Curr. Ther. Res.* 13 (1971) 631–635.
- [2] P. Deniker, H. Loo, H. Cuhe, J.M. Roux, Abuse of pyrovalerone by drug addicts, *Ann. Med. Psychol.* 2 (1975) 745.
- [3] S. Gibbons, M. Zloh, An analysis of the 'legal high' mephedrone, *Bioorg. Med. Chem. Lett.* 20 (2010) 4135–4139.
- [4] Psychonaut WebMapping Research Group, MDPV Report, Institute of Psychiatry, King's College London, London, UK, 2009.
- [5] I.A. Ojanperä, P.K. Heikman, I.J. Rasanen, Urine analysis of 3,4-methylenedioxy-pyrovalerone in opioid-dependent patients by gas chromatography–mass spectrometry, *Ther. Drug Monit.* (2011), doi:10.1097/FTD.0b013e318208b693.
- [6] C. Sauer, F.T. Peters, C. Haas, M.R. Meyer, G. Fritschi, H. Maurer, New designer drug α -pyrrolidinovalerophenone (PVP): studies on its metabolism and toxicological detection in rat urine using gas chromatographic/mass spectrometric techniques, *J. Mass Spectrom.* 44 (2009) 952–964.
- [7] H.H. Maurer, T. Kraemer, D. Springer, R.F. Staack, Chemistry, pharmacology, toxicology and hepatic metabolism of designer drugs of the amphetamine (ecstasy), piperazine, and pyrrolidinovalerophenone types, *Ther. Drug Monit.* 26 (2004) 127–131.
- [8] S.D. Brandt, R.C.R. Wootton, G. De Paoli, S. Freeman, The naphyrone story: the alpha or beta-naphthyl isomer? *Drug Test. Anal.* (2010), doi:10.1002/dta.185.
- [9] F. Schifano, A. Albanese, S. Fergus, J.L. Stair, P. Deluca, O. Corazza, Z. Davey, J. Corkery, H. Siemann, N. Scherbaum, M. Farre', M. Torrens, Z. Demetrovics, A.H. Ghodse, Psychonaut Web Mapping, ReDNet Research Group, Mephedrone (4-methylcathinone; 'meow meow'): chemical, pharmacological and clinical issues, *Psychopharmacology*, doi:10.1007/s00213.010.2070.x.
- [10] J.C. Yohannan, J.S. Bozenko Jr., The characterization of 3,4-methylenedioxy-pyrovalerone (MDPV), *Microgram J.* 7 (2010) 12–15.
- [11] F. Westphal, T. Junge, P. Rösner, F. Sönnichsen, F. Schuster, Mass and NMR spectroscopic characterization of 3,4-methylenedioxy-pyrovalerone: a designer drug with α -pyrrolidinovalerophenone structure, *Forensic Sci. Int.* 190 (2009) 1–8.
- [12] M.R. Meyer, P. Du, F. Schuster, H.H. Maurer, Studies on the metabolism of the α -pyrrolidinovalerophenone designer drug methylenedioxy-pyrovalerone (MDPV) in rat and human urine and human liver microsomes using GC–MS and LC–high-resolution MS and its detectability in urine by GC–MS, *J. Mass Spectrom.* 45 (2010) 1426–1442.
- [13] S. Strano-Rossi, A.B. Cadwallader, X. de la Torre, F. Botrè, Toxicological determination and *in vitro* metabolism of the new designer drug methylenedioxy-pyrovalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry, *Rapid Commun. Mass Spectrom.* 24 (2010) 2706–2714.
- [14] Europol–EMCDDA Joint Report on a New Psychoactive Substance: 4-Methylmethcathinone (Mephedrone).
- [15] S. Fröhlich, E. Lambe, J. O'Dea, Acute liver failure following recreational use of psychotropic "head shop" compounds, *Ir. J. Med. Sci.*, doi:10.1007/s11845.010.0636.6.
- [16] Elva åtalas i stor knarkhärva, Svenska Dagbladet, 22 October 2010, http://www.svd.se/nyheter/inrikes/elva-atalas-i-stor-knarkharva_5549347.svd (accessed 23.11.2010).
- [17] A.W. Jones, Age- and gender-related differences in blood amphetamine concentrations in apprehended drivers: lack of association with clinical evidence of impairment, *Addiction* 102 (2007) 1085–1091.
- [18] Richtlinien der GTFCh zur Qualitätssicherung forensisch-toxikogischer Untersuchungen vom 01.06.2009.
- [19] B. Güssregen, S. Schröfel, M. Nauck, T. Arndt, Selective Reaction Monitoring (SRM) Daten von mehr als 900 Xenobiotika für Aufbau und Validierung von LC–MS/MS Analysen, *Toxichem Krimtech* 75 (3) (2008) 149–174.
- [20] S. Schröfel, B. Güssregen, A. Werle, M. Nauck, T. Arndt, Selective Reaction Monitoring (SRM) Daten von Xenobiotika für Aufbau und Validierung von LC–MS/MS Analysen – Teil 2, *Toxichem Krimtech* 77 (2) (2010) 117–136.
- [21] DIN EN ISO/IEC 32645, 1994.
- [22] K.K. Karjalainen, T.P. Lintonen, A.O. Impinen, P.M. Lillsunde, A.I. Ostamo, Polydrug findings in drugged driving cases during 1977–2007, *J. Subst. Abuse* 15 (2010) 143–156.
- [23] A. Wohlfarth, W. Weinmann, Bioanalysis of new designer drugs, *Bioanalysis* 2 (2010) 965–979.
- [24] EMCDDA–Europol 2009 Annual Report on the Implementation of Council Decision 2005/387/JHA.
- [25] A.W. Jones, A. Holmgren, F.C. Kugelberg, Driving under the influence of central stimulant amines: age and gender differences in concentrations of amphetamine, methamphetamine and ecstasy in blood, *Traffic Inj. Prev.* 6 (2005) 317–322.

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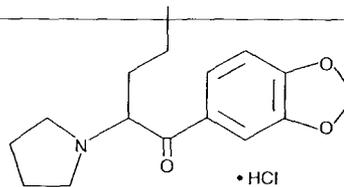
Product Information



Methylenedioxy Pyrovalerone (hydrochloride)

Item No. 10684

CAS Registry No.: 24622-62-6
Formal Name: 1-(1,3-benzodioxol-5-yl)-2-(1-pyrrolidinyl)-1-pentanone, monohydrochloride
Synonym: MDPV
MF: C₁₆H₂₁NO₃ • HCl
FW: 311.8
Purity: ≥98%
Stability: ≥2 years at -20°C ✓
Supplied as: A crystalline solid
UV/Vis.: λ_{max}: 234, 281, 318 nm



Laboratory Procedures

For long term storage, we suggest that methylenedioxy pyrovalerone (hydrochloride) (MDPV (hydrochloride)) be stored as supplied at -20°C. It should be stable for at least two years.

MDPV (hydrochloride) is supplied as a crystalline solid. A stock solution may be made by dissolving the MDPV (hydrochloride) in the solvent of choice. MDPV (hydrochloride) is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF), which should be purged with an inert gas. The solubility of MDPV (hydrochloride) in these solvents is approximately 1, 0.1, and 0.25 mg/ml in ethanol, DMSO and DMF, respectively.

Further dilutions of the stock solution into aqueous buffers or isotonic saline should be made prior to performing biological experiments. Ensure that the residual amount of organic solvent is insignificant, since organic solvents may have physiological effects at low concentrations. Organic solvent-free aqueous solutions of MDPV (hydrochloride) can be prepared by directly dissolving the crystalline solid in aqueous buffers. The solubility of MDPV (hydrochloride) in PBS, pH 7.2, is approximately 10 mg/ml. We do not recommend storing the aqueous solution for more than one day.

Pyrovalerone and its analogs are inhibitors of the transporters for certain monoamine neurotransmitters, including dopamine and norepinephrine, preventing their uptake.^{1,2} MDPV is an analog of pyrovalerone which includes the 3,4-methylenedioxy moiety found on 3,4-methylenedioxymethamphetamine (MDMA), a DEA Schedule I controlled substance. While its physiological, neurological, and toxicological actions have not been characterized, MDPV has been reported by the DEA to be abused as a central nervous system stimulant.³ Its effective dose and chemical interactions are unknown, but it has been used alone and in combination with other stimulating compounds. Products containing MDPV have been marketed in Europe and Australia; they have also been seized by law enforcement in several states.³ MDPV and some of its metabolites have recently been characterized by spectroscopic analysis.⁴⁻⁷ MDPV is to be used in the forensic analysis of samples that may contain this compound. This product, the hydrochloride salt of MDPV, has superior solubility in aqueous solvents, compared to the free base (Item No. 10624).

References

1. Heron, C., Costentin, J., and Bonnet, J.-J. *Eur. J. Pharmacol.* **264**, 391-398 (1994).
2. Meltzer, P.C., Butler, D., Deschamps, J.R., et al. *J. Med. Chem.* **49**(4), 1420-1432 (2006).
3. Drug Enforcement Admin. Office of Diversion Control Retrieved 2010, from http://www.deadiversion.usdoj.gov/drugs_concern/mdpv.pdf.
4. Westphal, F., Junge, T., Rosner, P., et al. *Forensic Sci. Int.* **190**, 1-8 (2009).
5. Meyer, M.R., Du, P., Schuster, F., et al. [In Press] *J. Mass Spectrom.* (2010).
6. Yohannan, J.C. and Bozenko, J.S. *Microgram Journal* **7** (1), 12-15 (2010).
7. Strano-Rossi, S., Cadwallader, A.B., de la Torre, X., et al. *Rapid Commun. Mass Spectrom.* **24**, 2706-2714 (2010).

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(734) 971-3335

Fax

(734) 971-3640

E-Mail

custserv@caymanchem.com

Web

www.caymanchem.com

The Characterization of 3,4-Methylenedioxypropylvalerone (MDPV)

Joshua C. Yohannan¹ and Joseph S. Bozenko, Jr.

U.S. Department of Justice
Drug Enforcement Administration
Special Testing and Research Laboratory
22624 Dulles Summit Court
Dulles, VA 20166

[Joshua.C.Yohannan -at- usdoj.gov and Joseph.S.Bozenko -at- usdoj.gov]

ABSTRACT: The analysis and characterization of 3,4-Methylenedioxypropylvalerone (MDPV) is presented. Gas chromatography/mass spectrometry (GC/MS), Fourier transform nuclear magnetic resonance (FTNMR) spectroscopy, solid phase Fourier transform infrared (FTIR) spectroscopy, and ultraviolet (UV) spectrophotometry data are presented.

KEYWORDS: MDPV, phenethylamines, GC/MS, FTNMR, FTIR, ultraviolet, forensic chemistry

In March 2008, police seized a small plastic bag labeled "1-(3,4-methylenedioxy-phenyl)-2-pyrrolidin-1-yl-pentan-1-one GC/MS Sample Not for Human Consumption." There was no lot number or manufacturer name on the bag. The bag contained 0.4 g of a white powdery substance that provided no match to available GC/MS libraries. The seizure was in response to a call for a vehicle off the road and stuck in the mud. The responding officer found the driver to be incoherent and confused; the driver subsequently failed a field sobriety test. The driver was requested to take a breathalyzer, which resulted in 0.00 Blood Alcohol Content. The driver declined a request for a blood test. It is not known whether the driver's condition was a direct result of MDPV intoxication. A search of the driver provided the above mentioned bag along with pharmaceutical tablets believed to be from India. The driver stated that he was a self-employed chemist and that was the reason that he was allowed to have the bag of white powder. The tablets included 98 promethazine HCl, 1 triazolam, 2 risperidone, 4 methocarbamol, 10 baclofen, 6 bromazepam, and 4 quetiapine fumarate tablets. Also recovered were a pill crusher and a prescription bottle containing residue.

MDPV and MDPK are both abbreviations for 3,4-Methylenedioxypropylvalerone (Figure 1). MDPV was first synthesized as part of a class of stimulants in 1969. MDPV is the methylenedioxy analogue of pyrovalerone, a Schedule V stimulant first synthesized in 1964. Pyrovalerone, available under the trade names Centroton and Thymergix, is used as an appetite suppressant or for the treatment of chronic fatigue.

MDPV is currently unscheduled in the United States. MDPV is found as a white or light tan powder. Users report the development of an odor when left exposed to the air. There are currently no known studies on the effects of MDPV on humans or on proper dosing. MDPV is commonly described as boosting a user's libido, however it is also associated with extreme anxiety at higher dosages. There are no known deaths due to the use of MDPV.

Experimental

Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectrum (Figure 2) was acquired using a Thermo-Nicolet Magna 560 spectrophotometer with a SensIR Dura-scope attenuated total reflectance (ATR) accessory. The spec-

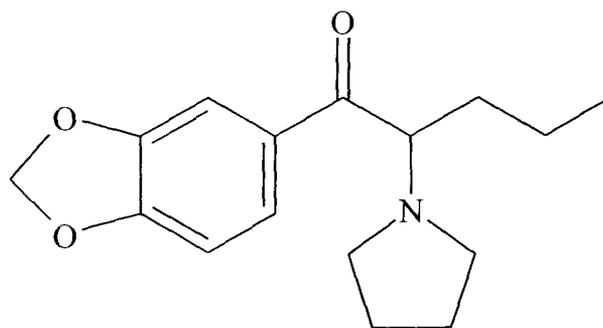


Figure 1 - 3,4-Methylenedioxypropylvalerone hydrochloride

Chemical Formula: $C_{16}H_{22}ClNO_3$

CAS Number: [24622-62-6]

Molecular Weight: 311.80 amu (as hydrochloride)

Melting Point: 238 - 239 °C with decomposition

Solubility (as hydrochloride): [Chloroform: Soluble;

Methanol: Soluble; Deionized H_2O : Soluble]

trum was collected using 32 scans between 4000 cm^{-1} and 400 cm^{-1} .

Gas Chromatography/Mass Spectrometry (GC/MS)

The mass spectrum (Figures 3a-3b) was acquired using an Agilent Model 6890N GC equipped with an Agilent Model 5973 quadrupole mass-selective detector (MSD). The MSD was operated using 70 eV E.I. The GC was fitted with a 30 m x 0.25 mm I.D. fused silica capillary column coated with 0.50 μm 35% phenyl, 65% dimethyl arylene siloxane (DB-35MS), and was operated in splitless mode. The injection port was maintained at 250°C. The oven temperature program was as follows: Initial temperature 90°C (1 min), ramped to 300°C at 8°C/min (final hold 10 min). Helium was used as a purge gas at a rate of 60 mL/sec. Methanol was used as the solvent.

Nuclear Magnetic Resonance (NMR) Spectroscopy

1H - and ^{13}C -NMR spectra (see Table 1, Figures 4 and 5, respectively) were acquired at 25°C on a Varian Mercury Plus 400 MHz instrument using a Nalorac 5 mm indirect detect pulse field gradient (PFG) probe. (1H parameters: Number of scans (nt) = 8, pulse width (pw) = 45°, relaxation delay

(d1) = 5 s, acquisition time (at) = 2.5 s; ^{13}C parameters: nt = 4098, pw = 45° , d1 = 1 s, at = 1.3 s, complete proton decoupled). Spectra were processed using ACD/Labs *SpecManager* software (Advanced Chemistry Development Inc., Toronto, Canada). MDPV was prepared with D_2O containing 5 mg/mL maleic acid (as internal standard) containing 0.05 wt % 3-trimethylsilyl-propionic-2,2,3,3- d_4 acid, sodium salt (TSP; Aldrich Chemical Co., Milwaukee, WI) at 16.87 mg/mL.

Chemical shifts (δ) are reported in parts per million (ppm) using TSP (0.0 ppm) as the reference standard (400 MHz, D_2O).

Ultraviolet (UV) Spectrophotometry

The UV spectrum (Figure 7) was acquired using a Hewlett-Packard 845x spectrophotometer with a 1 cm cell path length. The range scanned was 220-330 nm. The sample was dissolved in methanol.

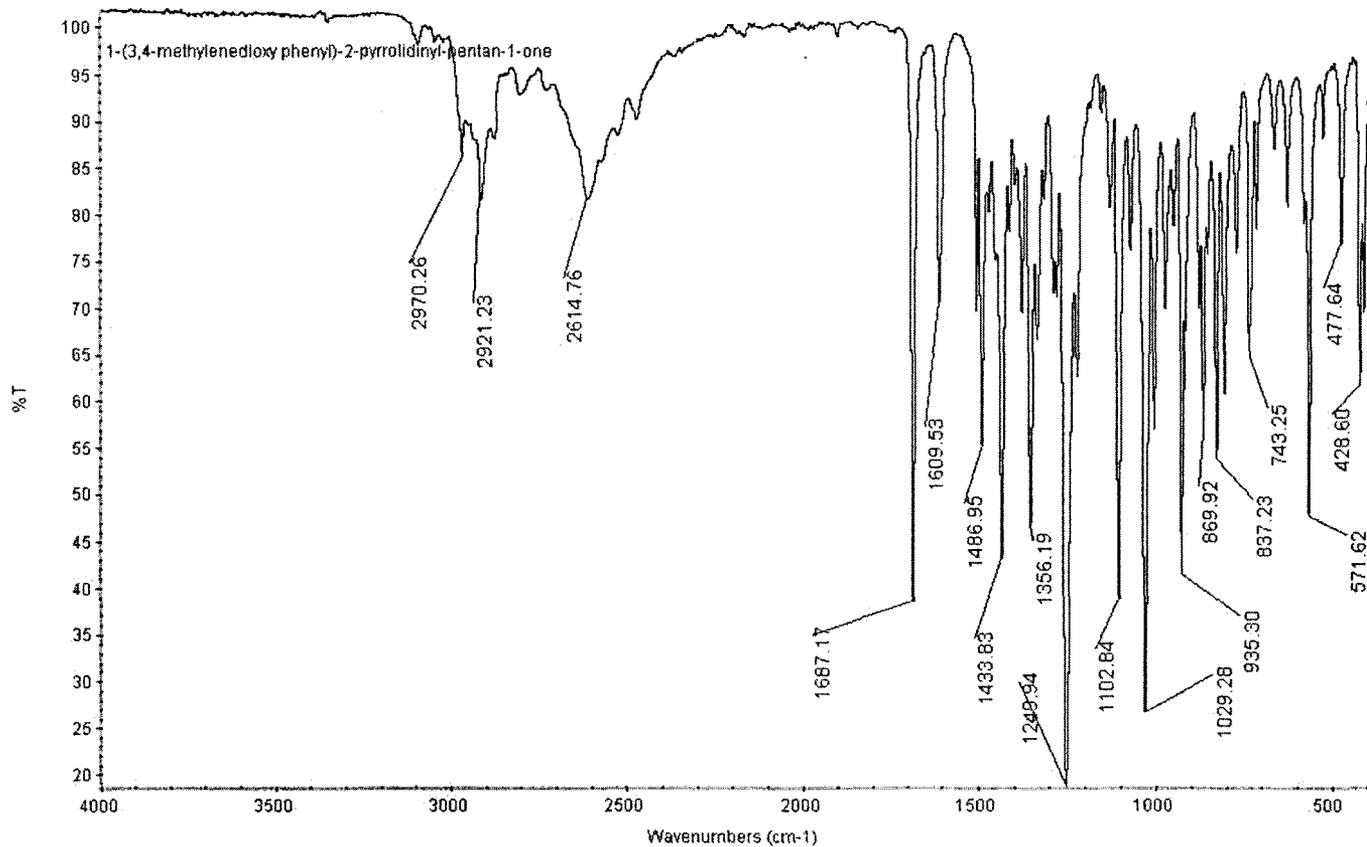


Figure 2 - FTIR-ATR spectrum of MDPV hydrochloride.

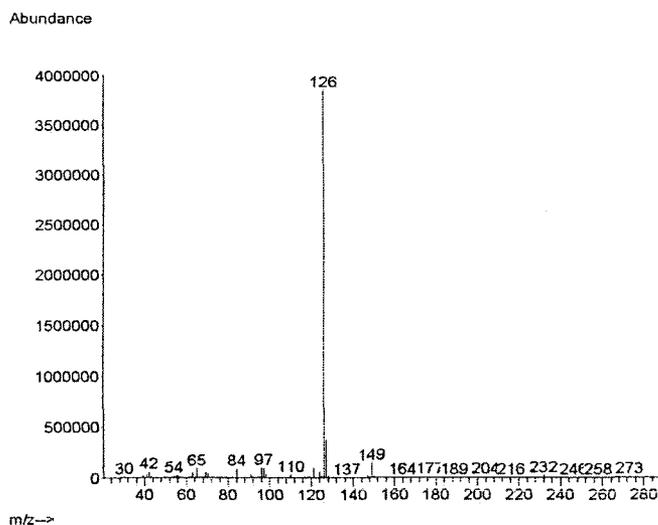


Figure 3a - E.I. mass spectrum of MDPV.

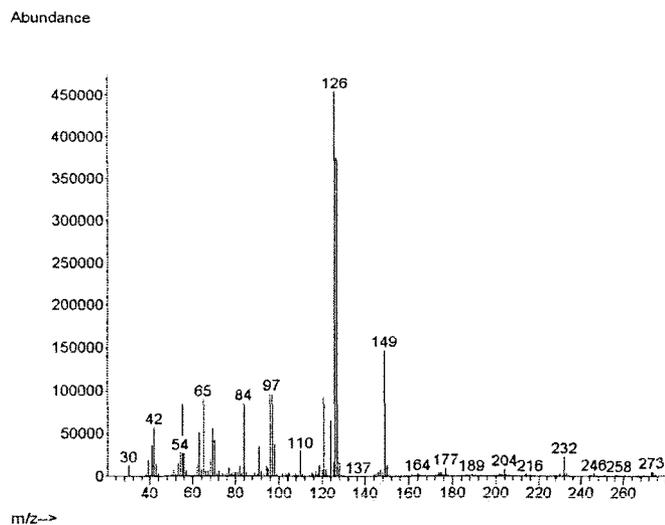


Figure 3b - Expanded E.I. mass spectrum of MDPV.

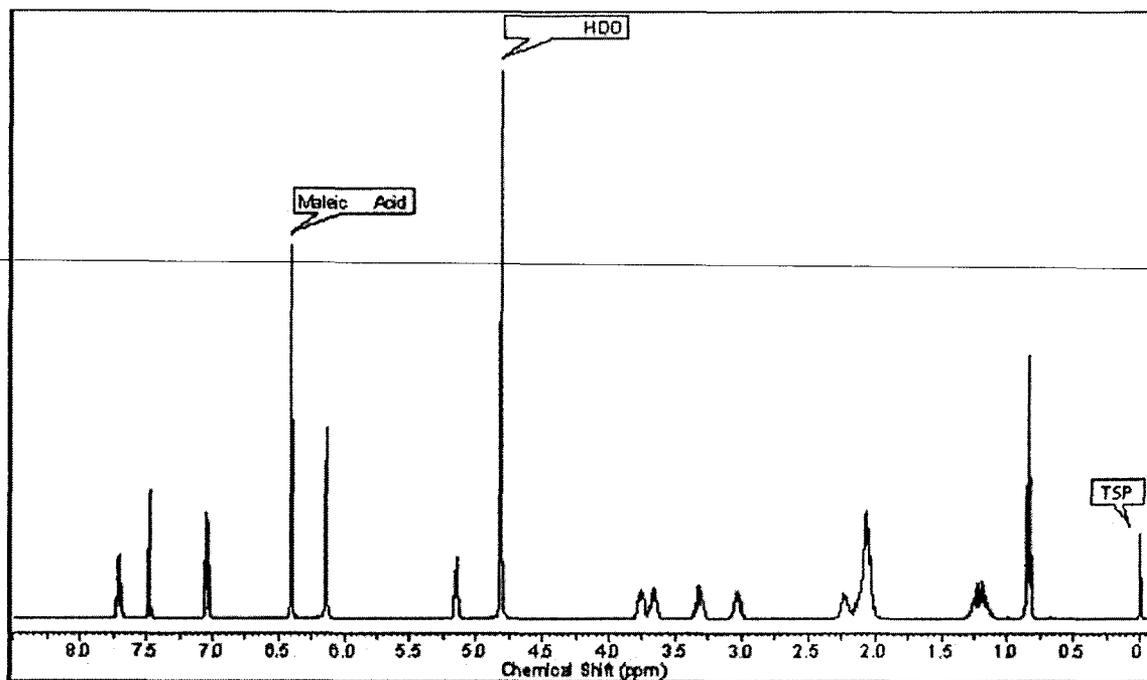


Figure 4 - 400 MHz FTNMR ¹H spectrum of MDPV in D₂O with maleic acid.

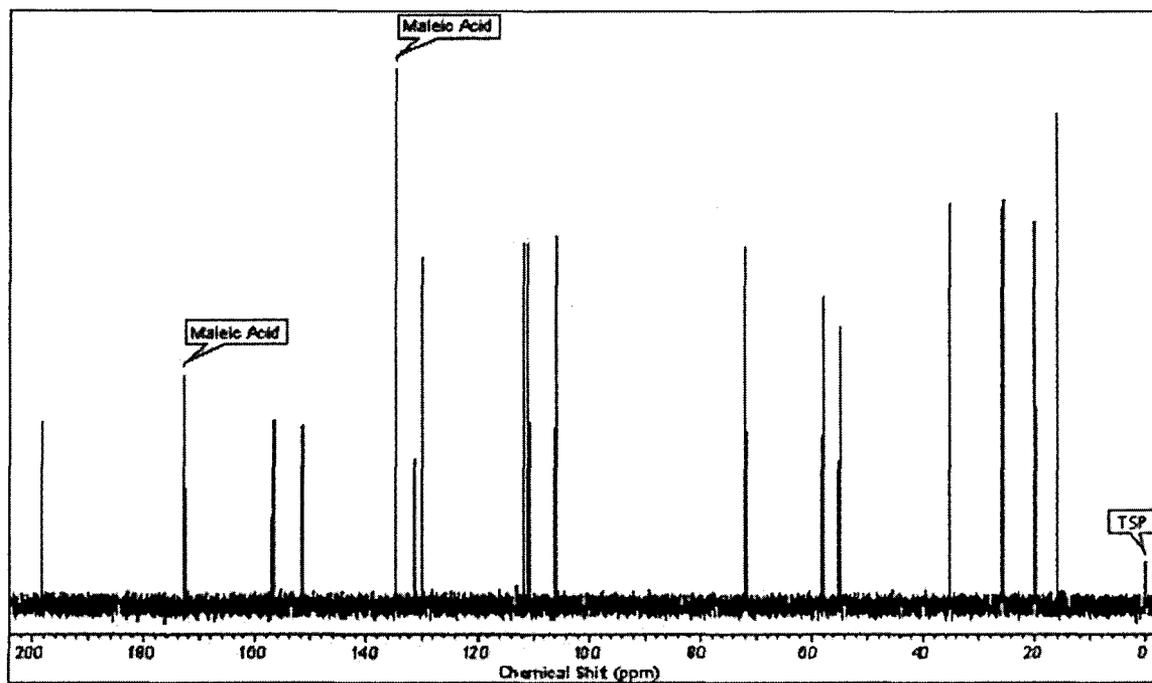


Figure 5 - 400 MHz FTNMR ¹³C spectrum of MDPV in D₂O with maleic acid.

Results and Discussion

The MDPV mass spectrum demonstrates similarity to other amines in that it gives a low-detail mass spectral fragmentation pattern. The base ion, *m/z* 126, however, is somewhat uncommon in drug analysis, which may prove to be of value in identifying MDPV. The resultant FTIR spectrum is very detailed with a number of sharp bands in the fingerprint region

that should enable relatively facile identification. Specifically, MDPV has proven to be an analyte that is easily distinguishable from other structurally related compounds.

References

1. 1-[(3,4-Methylenedioxy)phenyl]-2-pyrrolidino-1-alkanones as stimulants. (Boehringer Ingelheim Study) 1969.

Table 1 - Assignments, Multiplicities, and Coupling Constants.

Position	¹³ C (ppm)	¹ H (ppm)	Multiplicity	J (Hz)
Methylenedioxyphenyl - 2	105.71	6.14	multiplet	-
Methylenedioxyphenyl - 4	110.80	7.47	doublet	1.7
Methylenedioxyphenyl - 7	111.61	7.03	doublet	8.3
Methylenedioxyphenyl - 6	129.76	7.70	dd	1.7, 8.3
Methylenedioxyphenyl - 5	131.16	-	-	-
Methylenedioxyphenyl - 7a and 3a	151.50	-	-	-
	156.84	-	-	-
Sidechain - 1	198.36	-	-	-
Sidechain - 2	71.91	5.15	triplet	5.4
Sidechain - 3	35.16	2.06	multiplet	-
Sidechain - 4	19.94	1.24	multiplet	-
		1.17	multiplet	-
		0.83	triplet	7.3
Sidechain - 5	16.00	0.83	triplet	7.3
Pyrrolidine - 2 and 5	58.04	3.67	multiplet	-
		3.03	ddd	11.6, 8.0, 7.87
		3.76	multiplet	-
		3.32	multiplet*	9.5
Pyrrolidine - 3 and 4	25.80	2.22	multiplet	-
		2.06	multiplet	-
		2.06	multiplet	-
		2.06	multiplet	-

*apparent quartet

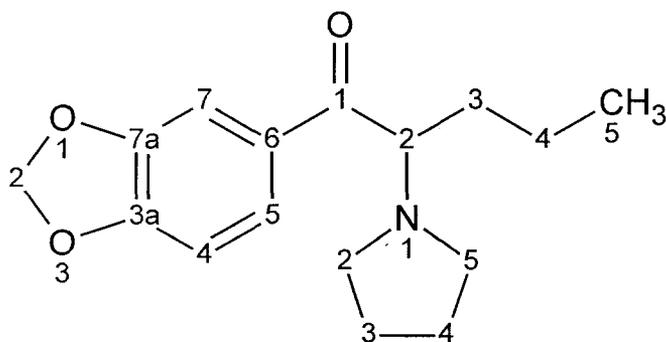


Figure 6 - Position of protons for MDPV (See Table 1).

- Heffe, W. Die Stevens-umlagerung von allyl-phenacyl-ammoniumsalzen. *Helv Chim Acta* 1964;47:1289-1292.
- Gardos G, Cole JO. Evaluation of pyrovalerone in chronically fatigued volunteers. *Curr Ther Res Clin Exp.* 1971;13(10):631-5.
- <http://en.wikipedia.org/wiki/MDPV> (cited Feb. 5, 2009)

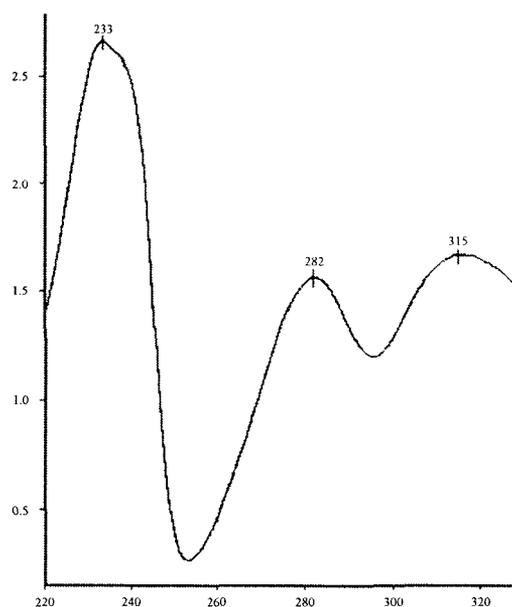


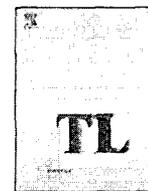
Figure 7 - Ultraviolet-visible spectrum of MDPV in methanol.



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Mini review

3,4-Methylenedioxypropylvalerone (MDPV): Chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online

M. Coppola^{a,*}, R. Mondola^b

^a Department of Addiction, ASL CN2, Viale Coppino 46, 12051, Alba (CN), Italy

^b Department of Mental Health, ASL CN1, Via Torino 70/B, 12037 Saluzzo (CN), Italy

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ABSTRACT

The illicit marketplace of substances of abuse continually offers for sale legal alternatives to controlled drugs to a large public. In recent years, a new group of designer drugs, the synthetic cathinones, has emerged as a new trend, particularly among young people. The 3,4-methylenedioxypropylvalerone (MDPV), one of this synthetic compounds, caused an international alert for its cardiovascular and neurological toxicity. This substance, sold as bath salts, has caused many serious intoxications and some deaths in several countries. The aim of this paper is summarise the clinical, pharmacological and toxicological information about this new designer drug.

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Contents

1. Introduction	12
2. Synthetic cathinones, <i>Catha edulis</i> (khat) and natural cathinones	13
2.1. Synthetic cathinones	13
2.2. <i>Chata edulis</i> (khat) and natural cathinones	13
3. 3,4-Methylenedioxypropylvalerone (MDPV)	13
3.1. Chemistry	13
3.2. Pharmacology	13
3.3. Toxicology	13
4. Internet information	14
5. Legal status	14
6. Discussion	14
7. Conclusion	14
Conflict of interest statement	14
References	14

1. Introduction

The illicit marketplace of substances of abuse continually offers for sale legal alternatives to controlled drugs to a large public. These psychoactive substances are both synthetic derivatives and vegetable compounds that can produce important public health consequences and policy implications (Collins, 2011). Furthermore, the internet has emerged as a new marketplace for the spread

of these products and its monitoring is an important instrument to identify new trends of drugs of abuse (Schifano et al., 2010). Recent information have shown that the online market is able to respond rapidly to changes in the legal status of the psychoactive drugs offering for sale new legal alternatives (Walsh, 2011). After the development of synthetic derivatives based on fentanyl in the 1980s, ring-substituted phenethylamines in the late 1980s, tryptamines in 1990s and piperazines in the 2000s, in recent years, a new group of designer drugs, the synthetic cathinones, has emerged as a new trend, particularly among young people (Brandt et al., 2010). Synthetic cathinones are a group of synthetic derivatives of the vegetable cathinone, a phenylalkylamine

* Corresponding author. Tel.: +39 0173316210; fax: +39 0173420344.
E-mail address: coppolamail@alice.it (M. Coppola).

alkaloid naturally present in the *Catha edulis* (khat) (Hassan et al., 2007). The first synthetic cathinone which has had a large diffusion in the population was the maphedrone, a psychoactive substance that has produced many serious intoxication and some deaths in various countries (Hadlock et al., 2011). When the legal status of this compound changed, another synthetic cathinone, the 3,4-methylenedioxypropylvalerone (MDPV), received a large diffusion among young people causing a new international alert (ISS, 2011). The aim of this paper is summarise the clinical, pharmacological and toxicological information about this new designer drug.

2. Synthetic cathinones, *Catha edulis* (khat) and natural cathinones

2.1. Synthetic cathinones

Synthetic cathinones are the beta-keto analogues of the natural cathinone, one of the psychoactive compounds present in khat, in particular, most of the synthetic cathinones appeared in the recreational drug market since the mid-2000s are a ring-substituted cathinone closely related to the phenethylamine family, differing only by a keto functional group at the beta carbon (namsdl, 2011). Like the related phenethylamines, synthetic cathinones can exist in two stereoisomeric forms that may have different potency and it is likely that some ring-substituted derivatives could be racemic mixtures (Gibbons and Zloh, 2010). Synthetic cathinones produce amphetamine-like effects because they inhibit the reuptake of and stimulate the release of norepinephrine, serotonin and dopamine (Cozzi et al., 1999; Kehr et al., 2011). These molecules are used as substitute for other stimulants such as amphetamines, cocaine or ecstasy because, although they are generally less lipophilic and less able to cross the blood–brain barrier (pyrrolidine derivatives such as pyrovalerone or MDPV are more lipophilic and more able to cross the blood–brain barrier than other synthetic cathinones), they can produce the same effects on the Central Nervous System (Dargan et al., 2011). The studies on the metabolism of cathinone derivatives in rats and humans have shown that they are N-demethylated, the keto group is reduced to hydroxyl and ring alkyl groups are oxidised (Meyer and Maurer, 2010). The users can snort or ingest these white or brown amorphous or crystalline powders, but since they are soluble in water, these substances can also be injected (Winstock et al., 2011; Schifano et al., 2011). In recent years, the assumption of synthetic cathinones has been associated with several cases of toxicity and deaths (James et al., 2010). Clinical features include neurological, cardiovascular and psychopathological symptoms such as: psychomotor agitation, delusions, hallucinations, psychosis, hypertension, palpitation, chest pain, seizures, headaches (Wood et al., 2010). Synthetic cathinones include several substances that have been used as research chemical, but only three compounds are used as medicinal products: amfepramone (obesity), pyrovalerone (obesity and chronic fatigue) and bupropion (depression and tobacco dependence), the others are used only for recreational scope (pharmacocode-amfepramone, 2011; pharmacocode-bupropion, 2011; Gordons and Cole, 1971).

2.2. *Chata edulis* (khat) and natural cathinones

Chata edulis, simply called khat, is an evergreen slow-growing shrub or tree native to Ethiopia and cultivated in East Africa and South West Arabian Peninsula that in recent years has been widespread in Europe too (emccda, 2011). The people living in khat geographical areas use the fresh vegetable material (leaves, stems, flower buds) of this plant for its stimulant effects (Kalix, 1992). The fresh khat leaves contain 62 alkaloids and for two of these, cathine

and cathinone, have been demonstrated amphetamine-like effects, particularly, these phenylalkylamine alkaloids cause the release of catecholamines from pre-synaptic storage sites in the central and peripheral nervous system (Kalix, 1986). In addition, these alkaloids may also have monoamine oxidase inhibition effects (Nencini et al., 1984). Cathine and cathinone determine in humans increased in blood pressure and in heart rate, euphoria and psychomotor hyperactivity (Brenneisen et al., 1990). Several studies have shown the harmful effects of this plant such as: increased incidence of acute coronary vasospasm and myocardial infarction, oesophagitis, gastritis, oral keratotic lesions and liver toxicity (Al-Habori, 2005). Furthermore, insomnia, depression, anorexia, psychosis and impaired working memory have been reported after occasional or chronic use of khat (Balint et al., 2009; Colzato et al., 2011).

3. 3,4-Methylenedioxypropylvalerone (MDPV)

3.1. Chemistry

The MDPV is a pyrrolidine derivative of the synthetic cathinone pyrovalerone differing for the presence of a 3,4-methylenedioxy group linked to the aromatic ring in substitution of a 4-methyl group (Yohannan and Bozenko, 2010) that was synthesized by Boehringer Ingelheim and patented in 1969 and first seized in German in the year 2007 (Westphal et al., 2009). This compound, IUPAC name 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-ylpentan-1-one, is a white (HCL salt form), brown or yellow-green (free base form) or gray (european form) amorphous or crystalline powder with a molecular weight of 275.34284 g/mol classified as a research chemical (pubchem, 2011). The MDPV includes in its chemical structure a nitrogen atom attached to three carbon atoms composing a tertiary amino group that is responsible of the high solubility of this compound in organic solvents, in particular the free base (caymanchem, 2011).

3.2. Pharmacology

Like pyrovalerone, MDPV is a monoamine uptake inhibitor more lipophilic and more potent than other cathinone derivatives (Meltzer et al., 2006). The high lipophilicity of this substance is caused by the pyrrolidine ring and the tertiary amino group creating a less polar molecule more able to cross the blood–brain barrier (emccda, 2010). The metabolism of MDPV was evaluated in vitro using human liver microsomes and S9 cellular fractions for CYP450 phase I and uridine 5-diphosphoglucuronosyltransferase and sulfotransferase for the phase II metabolism. This study has demonstrated that the main metabolites of MDPV are catechol and methyl-catechol pyrovalerone which are in turn sulfated and glucuronated (Strano-rossi et al., 2011).

3.3. Toxicology

There are limited information about the short and long-term toxicological effects of this designer drug of abuse. The action of MDPV on monoamine reuptake may produce stimulant effects like cocaine, amphetamines or ecstasy, particularly, the stimulant effect has been compared to methylphenidate, at low doses, and cocaine or amphetamines, at high doses (scribd, 2011). In literature have been reported acute toxicity episodes and deaths related to MDPV assumption in several countries (acep, 2011). Acute toxicity mainly includes neurological, cardiovascular and psychopathological symptoms such as: tachycardia, chest pain, S-T segment changes, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatism, parkinsonism, delusions, hallucinations, paranoid psychosis, depression, panic attacks,

long term changes in cognition and emotional stability, rhabdomyolysis, abdominal pain, vomiting, kidney damage (Durham, 2011; CDC, 2011; Penders and Gestring, 2011). The treatment generally includes low or moderate doses of a benzodiazepine to control the signs of toxicity and antipsychotics or propofol when this medicament is ineffective (Spiller et al., 2011). Furthermore, it was reported the development of craving, tolerance, dependence and withdrawal syndrome after the frequent consumption of high doses of MDPV (CDC, 2011). The MDPV is not detected via standard drug tests but it is required the gas chromatography/mass spectrometry (GS/MS) (Ojanpera et al., 2011).

4. Internet information

The online discussion about MDPV seems begun around 2004, but the popularity of this substance increased in late 2008 (drugguide, 2011; drugs-forum, 2011). Users reported soft Central Nervous System stimulant effects of MDPV at low doses, but very strong stimulant effects at high doses, more potent than cocaine or amphetamines (drugs-forum, 2011; erowid, 2011). There were many reports of people that have used low doses of MDPV to increase the concentration, capacity to work or study, sexual performance (drugs-forum, 2011; erowid, 2011). Other desired psychoactive effects include: increased sociability, energy, limited euphoria, mild empathogenic effects (drugrecognitionexpert, 2011). Users also reported untoward effects such as: prolonged panic attack, tremor, agitation, insomnia, nausea, headache, tinnitus, dizziness, increased heart rate, altered vision, confusion, suicidal thoughts, anhedonia, depression, psychosis, risk of tolerance and dependence (drugs-forum, 2011; erowid, 2011; zoklet, 2011). Internet information also reported some discussion about the combination of MDPV with other drugs in order to reduce the harmful effects or enhance the desired effects. In particular, the most discussed combination are between MDPV and alcohol, propranolol or other beta blocker (to counteract tachycardia) GHB, 5-MeO-MIPT (as an aphrodisiac), GBL, zopiclone (to produce visual hallucinations), kratom, hallucinogenes, amphetamines (to enhance stimulant and entactogen effects), pregabalin, famotidine, omeprazole, domperidone (to counteract stomach pain), opiates (speedball like-effects), cannabis, benzodiazepines (to counteract anxiety) and other synthetic compounds (e.g. mephedrone, methylone) (drugs-forum, 2011). The modalities of administration include: oral ingestion, sublingual, intravenous, intramuscular, smoking, insufflation (snorting), inhalation and it has been reported the rectal administration (drugs-forum, 2011; erowid, 2011). Independently of the modalities of intake, the psychoactive effects may be the same, but non-oral assumption could produce shorter duration of action (drugs-forum, 2011). Some users suggest that 1 mg or 2 mg of MDPV are able to produce psychoactive effects (sublingual, rectal or inhalation assumption), but the typical doses range appear to be between 5 and 30 mg in a single ingestion. Redosing in a single session is very common because MDPV have a short duration of action (doses higher to 200 mg in a single session have been reported) (drugs-forum, 2011; bluelight, 2011; erowid, 2011).

5. Legal status

The MDPV is not approved as therapeutic drug and it is a controlled substance in Sweden (2010), Denmark (2009), Ireland (2010), United Kingdom (2010), Germany (2010), Australia (2010), Finland (2010), Israel and Italy. In addition this substance is controlled in some States of United States of America such as: Alabama, Florida, Idaho, Louisiana, Michigan, Mississippi, New Jersey, North Carolina, North Dakota and Utah (2011) (sostanze.info, 2011; drugs-forum, 2011).

6. Discussion

The MDPV is a catecholamines reuptake inhibitor derived by pyrovalerone with strong stimulant effects. This compound, classified as research chemical, can be considered a new designer drug of abuse. Little is known about the clinical, pharmacological and toxicological effects of MDPV, but some reports and the information on drugs forum suggest that its stimulant action could be more potent than cocaine or amphetamines. These psychoactive effects may justify the widespread of this compound as recreational drug, particularly among young people. Furthermore, the legal status of MDPV in several countries, the wide availability on the online market and the difficulty of identification in biological materials have favored the use of this synthetic cathinone as alternative to other illicit stimulants. Finally, the marketing of MDPV as bath salts or plants fertilizer provided false assurances on the safety of this substance as drug of abuse. The literature data and internet information have shown the high Cardiovascular and Central Nervous Systems acute toxicity of MDPV related to the powerful stimulation of the catecholaminergic system (Meltzer et al., 2006; Durham, 2011). Furthermore, the dopaminergic stimulation in the reward system could explain the development of tolerance, abuse, dependence and withdrawal syndrome reported by users (Ross and Peselow, 2009). Thus, considering the limited information about the clinical, pharmacological and toxicological effects of this substance in combination with the potential health risks, the alertness of scientific community is of great importance in order to monitoring and prevent the spread of MDPV.

7. Conclusion

In this paper we reviewed literature data and internet information about the clinical, pharmacological and toxicological effects of MDPV. Although this substance is marketed as bath salts or plants fertilizer, the drug users utilize the MDPV for its cocaine and amphetamine-like effects. Furthermore, in several countries MDPV is a legal alternative to illicit stimulants used by people that are afraid of the judicial consequences of the controlled substances assumption. Clinical reports and internet information clearly demonstrate the acute Cardiovascular and Central Nervous Systems toxicity of MDPV in combination with the high risk of death drug-related, abuse, tolerance and dependence. Scientific community must monitorate the diffusion of MDPV and it should use the information on drugs forum to identify new trends of substances of abuse early. In conclusion, the data currently available suggest that the recreational use of MDPV must be considered highly dangerous to public health.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

- Al-Habori, M., 2005. The potential adverse effects of habitual use of *Catha edulis* (khat). *Expert Opin. Drug. Saf.* 4, 1145–1154.
- Balint, E.E., Falkay, G., Balint, G.A., 2009. Khat—a controversial plant. *Wien. Klin. Wochenschr.* 121, 604–614.
- Brenneisen, R., Fisch, H.V., Koelbing, V., Geissshusler, S., Kalix, P., 1990. Amphetamine-like effect in humans of the khat alkaloid cathinone. *Br. J. Clin. Pharmacol.* 30, 825–828.
- Brandt, S.D., Freeman, S., Summale, H.R., Measham, F., Cole, J., 2010. Analysis of NRG “Legal highs” in the UK: identification and formation of novel cathinones. *Drug Test. Anal.* 2, 377–382.
- Centers For Disease Control and Prevention (CDC), 2011. Emergency department visits after use of a drug sold as “bath salts”—Michigan, November 13, 2010–March 31, 2011. *MMWR Morb. Mortal. Wkly. Rep.* 60, 624–627.
- Collins, M., 2011. Some new psychoactive substances: precursor chemicals and synthesis-driven and -products. *Drug Test. Anal.* 3, 404–416.

- Colzato, L.S., Ruiz, M.J., Van den Wildenberg, W.P.M., Hommel, B., 2011. Khat use is associated with impaired working memory and cognitive flexibility. *PLoS One* 6, e20602.
- Cozzi, N.V., Sievert, M.K., Shulgin, A.T., Jacob III, P., Ruoho, A.E., 1999. Inhibition plasma membrane monoamine transporters by beta-ketoamphetamines. *Eur. J. Pharmacol.* 381, 63–69.
- Dargan, P.I., Sedefov, R., Gallegos, A., Wood, D.M., 2011. The pharmacology and toxicology of the synthetic cathinone mephedrone (4-methylmethcathinone). *Drug Test. Anal.* 3, 454–463.
- Durham, M., 2011. Ivory wave: the next mephedrone? *Emerg. Med. J.* doi:10.1136/emj.2011.1129.20.
- Gibbons, S., Zloh, M., 2010. An analysis of 'legal high' mephedrone. *Bioorg. Med. Chem. Lett.* 20, 4135–4139.
- Gordons, G., Cole, J.O., 1971. Evaluation of pyrovalerone in chronically fatigued volunteers. *Curr. Ther. Res.-Clin. Exp.* 13, 631–635.
- Hadlock, G.C., Webb, K.M., McFadden, L.M., Chu, P.W., Ellison, J.D., Allen, S.C., et al., 2011. 4-Methylmethcathinone (mephedrone): neuropharmacological effects of a designer stimulant of abuse. *J. Pharmacol. Exp. Ther.* doi:10.1124/jpet.111.184119.
- Hassan, N.A., Gunaid, A.A., Murray-Lyon, I.M., 2007. Khat (*Catha edulis*): health aspects of khat chewing. *East Mediterr. Health J.* 13, 706–718. <http://www.acep.org/Content.aspx?id=77160> (visited August 14, 2011). <http://www.bluelight.ru> (visited August 17, 2011). <http://www.caymanchem.com/pdfs/10624.pdf> (visited September 29, 2011). <http://www.drugguide.us/mdpv/encyclopedia.htm#effects> (visited August 15, 2011). <http://www.drugrecognitionexpert.us/2011/02/bath-salts-mdpv/> (visited September 29, 2011). <http://www.drugs-forum.com> (visited August 17, 2011). <http://www.emcdda.europa.eu/publications/drug-profiles/khat> (visited August 11, 2011). <http://www.emcdda.europa.eu/publication/drug-profiles/syntetic-cathinones> (visited August 11, 2011). <http://www.erowid.org> (visited August 17, 2011). <http://www.iss.it/ssps/riii/cont.php?id=2056&lang=1&tipo=2> (visited August 14, 2011). <http://www.namsdl.org/documents/ACMDCathinonesReport.pdf> (visited August 14, 2011). <http://pharmacycode.com/amphepramone.html> (visited August 13, 2011). <http://pharmacycode.com/bupropion.html> (visited August 14, 2011). <http://www.pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=20111961> (visited August 14, 2011). <http://www.scribd.com/doc/57078733/Bath-Salt> (visited August 14, 2011). <http://www.sostanze.info/sites/default/files/documenti/Scheda.tecnica.MDPV.pdf> (visited August 16, 2011). <http://www.zoklet.net> (visited August 17, 2011).
- James, D., Adams, R.D., Spears, R., Cooper, G., Lupton, D.J., Thompson, J.P., et al., 2010. Clinical characteristics of mephedrone toxicity reported to the UK National Poison Information Service. *Emerg. Med. J.* 28, 686–689.
- Kalix, P., 1986. The releasing effect of the alkaloid cathinone at centre and peripheral catecholamine storage sites. *Neuropharmacology* 25, 499–501.
- Kalix, P., 1992. Chatinone, a natural amphetamine. *Pharmacol. Toxicol.* 70, 77–86.
- Kehr, J., Ichinose, F., Yoshitake, S., Gojny, M., Silvertsson, T., Nyberg, F., et al., 2011. Mephedrone compared to MDMA (ecstasy) and amphetamine rapidly increases both dopamine and serotonin levels in nucleus accumbens of awake rats. *Br. J. Pharmacol.* doi:10.1111/j.1476-5381.2011.01499.x.
- Meltzer, P.C., Butler, D., Deschamps, R., Madras, B.K., 2006. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J. Med. Chem.* 49, 1420–1432.
- Meyer, M.R., Maurer, H.H., 2010. Metabolism of designer drugs of abuse: an updated review. *Curr. Drug Metab.* 11, 468–482.
- Nencini, P., Amiconi, G., Befani, O., Abdullahi, M.A., Anania, M.C., 1984. Possible involvement of amine oxidase inhibition in the sympathetic activation by khat (*Catha edulis*) chewing in humans. *J. Ethnopharmacol.* 11, 78–86.
- Ojanpera, I.A., Heikman, P.K., Rasanen, I.J., 2011. Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography–mass spectrometry. *Ther. Drug. Monit.* 33, 257–263.
- Penders, T.M., Gestring, R., 2011. Hallucinatory delirium following use of MDPV: "Bath Salts". *Gen. Hosp. Psychiatry*, doi:10.1016/j.genhosppsych.2011.05.014.
- Ross, S., Peselow, E., 2009. The neurobiology of addictive disorders. *Clin. Neuropharmacol.* 32, 269–276.
- Schifano, F., Ricciardi, A., Corazza, O., Deluca, P., Davey, Z., Raffaelli, C., et al., 2010. New drugs of abuse on the web: the role of the Psychonaut Web Mapping Project. *Riv. Psichiatr.* 45, 88–93.
- Schifano, F., Albanese, A., Fergus, S., Stair, J.L., Deluca, P., Corazza, O., et al., 2011. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. *Psychopharmacology* 214, 593–602.
- Spiller, H.A., Ryan, M.L., Weston, R.G., Jansen, I.J., 2011. Clinical experience with analytical confirmation "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin. Toxicol.* 49, 499–505.
- Strano-rossi, S., Cadwallader, A.B., de la Torre, X., Botrè, F., 2011. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun. Mass Spectrom.* 24, 2706–2714.
- Walsh, C., 2011. Drugs, the internet and change. *J. Psychoactive Drugs* 43, 55–63.
- Westphal, F., Junge, T., Rosner, P., Sonnichsen, F., Schuster, F., 2009. Mass and NMR spectroscopic characterization of 3,4-methylenedioxypropylvalerone: a designer drug with alpha-pyrrolidinophenone structure. *Forensic Sci. Int.* 190, 1–8.
- Winstock, A.R., Mitcheson, L.R., Davey, Z., Corazza, O., Schifano, F., 2011. Mephedrone, new kid for the chop? *Addiction* 106, 154–161.
- Wood, D.M., Davies, S., Greene, S.L., Button, J., Holt, D.W., Ramsey, J., et al., 2010. Case series of individuals with analytically confirmed acute mephedrone toxicity. *Clin. Toxicol.* 48, 924–927.
- Yohannan, J.C., Bozenko, J.S., 2010. The characterisation of 3,4-methylenedioxypropylvalerone. *Microgram J.* 7, 12–15.



administrative law judge mails a notice of his or her hearing decision.

- 8. Amend § 416.1442 by revising paragraphs (d), (e) introductory text, (e)(1), and (f)(3) to read as follows:

§ 416.1442 Prehearing proceedings and decisions by attorney advisors.

* * * * *

(d) *Notice of a decision by an attorney advisor.* If an attorney advisor issues a fully favorable decision under this section, we will mail a written notice of the decision to all parties at their last known addresses. We will state the basis for the decision and advise all parties that they may request that an administrative law judge reinstate the request for a hearing if they disagree with the decision for any reason. Any party who wants to make this request must do so in writing and send it to us within 60 days of the date he or she receives notice of the decision. The administrative law judge will extend the time limit if the requestor shows good cause for missing the deadline. The administrative law judge will use the standards in § 416.1411 to determine whether there is good cause. If the request is timely, an administrative law judge will reinstate the request for a hearing and offer all parties an opportunity for a hearing.

(e) *Effect of an attorney advisor's decision.* An attorney advisor's decision under this section is binding unless—

- (1) You or another party to the hearing submits a timely request that an administrative law judge reinstate the request for a hearing under paragraph (d) of this section;

* * * * *

(f) * * *

- (3) Make the decision of an attorney advisor under paragraph (d) of this section subject to review by the Appeals Council if the Appeals Council decides to review the decision of the attorney advisor anytime within 60 days after the date of the decision under § 416.1469.

* * * * *

- 9. Amend § 416.1448 by revising the second sentence of paragraph (a), and paragraph (b)(1)(ii), to read as follows:

§ 416.1448 Deciding a case without an oral hearing before an administrative law judge.

(a) *Decision fully favorable.* * * *

The notice of the decision will state that you have the right to an oral hearing and to examine the evidence on which the administrative law judge based the decision.

(b) * * *

(1) * * *

- (ii) You live outside the United States, you do not inform us that you wish to

appear, and there are no other parties who wish to appear.

* * * * *

- 10. Revise § 416.1460 to read as follows:

§ 416.1460 Vacating a dismissal of a request for a hearing before an administrative law judge.

(a) Except as provided in paragraph (b) of this section, an administrative law judge or the Appeals Council may vacate a dismissal of a request for a hearing if you request that we vacate the dismissal. If you or another party wish to make this request, you must do so within 60 days of the date you receive notice of the dismissal, and you must state why our dismissal of your request for a hearing was erroneous. The administrative law judge or Appeals Council will inform you in writing of the action taken on your request. The Appeals Council may also vacate a dismissal of a request for a hearing on its own motion. If the Appeals Council decides to vacate a dismissal on its own motion, it will do so within 60 days of the date we mail the notice of dismissal and will inform you in writing that it vacated the dismissal.

(b) If you wish to proceed with a hearing after you received a fully favorable revised determination under the prehearing case review process in § 416.1441, you must follow the procedures in § 416.1441(d) to request that an administrative law judge vacate his or her order dismissing your request for a hearing.

[FR Doc. 2011-27236 Filed 10-20-11; 8:45 am]

BILLING CODE 4191-02-P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-357]

Schedules of Controlled Substances: Temporary Placement of Three Synthetic Cathinones Into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.
ACTION: Final Order.

SUMMARY: The Administrator of the Drug Enforcement Administration (DEA) is issuing this final order to temporarily schedule three synthetic cathinones under the Controlled Substances Act (CSA) pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). The substances are 4-methyl-N-methylcathinone (mephedrone), 3,4-

methylenedioxy-N-methylcathinone (methylone), and 3,4-methylenedioxypyrovalerone (MDPV). This action is based on a finding by the Administrator that the placement of these synthetic cathinones and their salts, isomers, and salts of isomers into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. As a result of this order, the full effect of the CSA and its implementing regulations including criminal, civil and administrative penalties, sanctions and regulatory controls of Schedule I substances will be imposed on the manufacture, distribution, possession, importation, and exportation of these synthetic cathinones.

DATES: Effective Date: This Final Order is effective on October 21, 2011.

FOR FURTHER INFORMATION CONTACT: Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone (202) 307-7165.

SUPPLEMENTARY INFORMATION:

Background

The Comprehensive Crime Control Act of 1984 (Pub. L. 98-473), which was signed into law on October 12, 1984, amended section 201 of the CSA (21 U.S.C. 811) to give the Attorney General the authority to temporarily place a substance into Schedule I of the CSA for one year without regard to the requirements of 21 U.S.C. 811(b) if he finds that such action is necessary to avoid imminent hazard to the public safety. 21 U.S.C. 811(h); 21 CFR 1308.49. If proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1), the Attorney General may extend the temporary scheduling up to an additional six months. 21 U.S.C. 811(h)(2). Where the necessary findings are made, a substance may be temporarily scheduled in Schedule I if it is not listed in any other schedule under section 202 of the CSA (21 U.S.C. 812) or if there is no exemption or approval in effect under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) for the substance. 21 U.S.C. 811(h)(1). The Attorney General has delegated his authority under 21 U.S.C. 811 to the Administrator of DEA. 28 CFR 0.100.

Section 201(h)(4) of the CSA (21 U.S.C. 811(h)(4)) requires the Administrator to notify the Secretary of Health and Human Services of her intention to temporarily place a substance into Schedule I of the CSA.¹

¹ Because the Secretary of Health and Human Services has delegated to the Assistant Secretary for

Continued

The Administrator transmitted notice of her intent to place mephedrone, methylone and MDPV in Schedule I on a temporary basis to the Assistant Secretary in a letter dated June 15, 2011. The Assistant Secretary responded to this notice by letter dated July 25, 2011, and advised that based on review by the Food and Drug Administration (FDA) there are currently no investigational new drug applications (INDs) or approved new drug applications (NDAs) for MDPV, mephedrone, or methylone. The Assistant Secretary also stated that the Department of Health and Human Services has no objection to the temporary placement of MDPV, mephedrone, and methylone into Schedule I of the CSA. DEA has taken into consideration the Assistant Secretary's comments. As MDPV, mephedrone, and methylone are not currently listed in any schedule under the CSA, as no exemptions or approvals are in effect for MDPV, mephedrone, and methylone under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), and as this temporary scheduling is necessary to avoid an imminent hazard to the public safety, DEA believes that the conditions of 21 U.S.C. 811(h)(1) have been satisfied.

A notice of intent to temporarily place mephedrone, methylone, and MDPV into Schedule I of the CSA was published in the *Federal Register* on September 8, 2011 (76 FR 55616). The data in support of the notice of intent and additional data continue to support the necessary findings to place mephedrone, methylone, and MDPV temporarily into Schedule I of the CSA as necessary to avoid an imminent hazard to the public safety.² In making this finding, the Administrator is required to consider three of the eight factors set forth in section 201(c) of the CSA (21 U.S.C. 811(c)). These factors are as follows: The substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(c)(4)-(6). Consideration of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

Health of the Department of Health and Human Services the authority to make domestic drug scheduling recommendations, for purposes of this Final Order, all subsequent references to "Secretary" have been replaced with "Assistant Secretary."

² See "Background, Data and Analysis of Synthetic Cathinones: Mephedrone (4-MMC), Methylone (MDMC) and 3,4-Methylenedioxypropylvalerone (MDPV)" found at <http://www.regulations.gov>.

Mephedrone, methylone, and MDPV are not currently listed in any schedule under the CSA. The temporary placement of these three synthetic cathinones into Schedule I of the CSA is necessary in order to avoid an imminent hazard to the public safety. First, there has been a rapid and significant increase in abuse of these substances in the United States. As a result of this abuse, synthetic cathinones are banned in at least 37 states in the United States and several countries, and all five branches of the U.S. military prohibit military personnel from possessing or using synthetic cathinones. Second, law enforcement has seized synthetic cathinones and, based on self-reports to law enforcement and health care professionals, synthetic cathinones are abused for their psychoactive properties. Third, federal, state and local public health departments and poison control centers have issued reports describing public health consequences such as emergency department visits and deaths from the use of these synthetic cathinones. Based on scientific data currently available, these three substances have the potential to be extremely harmful and, therefore, pose an imminent hazard to the public safety.

Factor 4: History and Current Pattern of Abuse

Synthetic cathinones are designer drugs of the phenethylamine class which are structurally and pharmacologically similar to amphetamine, 3,4-methylenedioxyamphetamine (MDMA), cathinone and other related substances. The addition of a beta-keto (β -keto) substituent to the phenethylamine core structure produces a group of substances that now have cathinone as the core structure. Synthetic cathinones, like amphetamine, cathinone, methcathinone, and methamphetamine, are central nervous system (CNS) stimulants.

The synthetic cathinones mephedrone, methylone, and MDPV have recently emerged on the United States' illicit drug market and are being perceived as being 'legal' alternatives to cocaine, methamphetamine, and MDMA. Although synthetic cathinones are new to the United States' illicit drug market, they have been popular drugs of abuse in Europe since 2007. MDPV is a derivative of pyrovalerone, which is a psychoactive drug that was used to treat chronic lethargy and fatigue. Research in anti-depressant and anti-parkinson agents resulted in the development and patenting of methylone. Methylone,

however, has not been approved for these purposes. There are no currently accepted medical uses in treatment in the United States for mephedrone, methylone, or MDPV.

Mephedrone, methylone, and MDPV are falsely marketed as "research chemicals," "plant food," or "bath salts." They are sold at smoke shops, head shops, convenience stores, adult book stores, and gas stations. They can also be purchased on the Internet and mailed using the U.S. Postal Service or international mail services. The packages of products containing these synthetic cathinones usually have the warning "not for human consumption," most likely in an effort to circumvent statutory restrictions for these substances. Despite disclaimers that the products are not intended for human consumption, retailers promote that routine urinalysis drug tests will not typically detect the presence of these synthetic cathinones. However, analytical methods for the detection of mephedrone, methylone, MDPV, and other synthetic cathinones have recently been developed for these substances.

Evidence indicates that mephedrone, methylone, and MDPV are being abused for their psychoactive properties. Drug surveys found that these and other synthetic cathinones are being used as recreational drugs and are used as alternatives to illicit stimulants like MDMA and cocaine. Accordingly, mephedrone, methylone, and MDPV have been identified in human urine samples that were obtained for routine drug screenings, they have been detected in samples from drivers suspected of driving under the influence, and they have been detected by drug courts during mandatory periodic drug screens. They have also been identified in biological specimens from individuals (some exhibiting symptoms of "extreme agitation" or "excited delirium") who have been arrested for possession of a controlled substance, child endangerment, or homicide. They have been detected in samples from decedents whose causes of death were reported as drug-induced toxicity, multiple drug toxicity, or other causes (e.g., blunt force trauma from a vehicular collision or suicide).

Based on studies in the scientific literature, the marketing of products that contain mephedrone, methylone, and MDPV is geared towards teens and young adults. Accordingly, reports indicate that the main users of synthetic cathinones are young male adults. These substances are also used by mid-to-late adolescents and older adults. Many of these abusers of synthetic cathinones have a previous history of drug abuse.

According to drug surveys, the reported average amount of synthetic cathinones used per dose ranged from approximately 25 to 250 milligrams and the average amount used per session (i.e., repeated administration and binging) ranged from approximately 25 milligrams to 5 grams depending on the substance consumed, duration of intake, and route of administration. The most common routes of administration of these substances are nasal insufflation by snorting the powder and oral ingestion by swallowing capsules or tablets. Other reported methods of administration include injection, rectal administration, and "bombing" (wrapping a dose of powder in a paper wrap and swallowing). Synthetic cathinones have also been reported to be used in binges. Reasons cited for binging include to prolong the duration of effects, to satisfy a "craving," or to satisfy a strong urge to re-dose.

According to information found in drug surveys, clinical case reports, and law enforcement reports, users have reported using products containing mephedrone, methylone, and MDPV with other synthetic cathinones (e.g., butylone, fluoromethcathinone, 4-MEC, etc.), pharmaceutical agents (e.g., lidocaine, caffeine, benzocaine, etc.), or other recreational substances (e.g., amphetamine, MDMA, cocaine, gamma-butyrolactone (GBL), kratom, N,N-benzylpiperazine (BZP), and 1-(3-trifluoromethylphenyl)-piperazine (TFMPP)). Chemical analyses of seized and purchased synthetic cathinone products indicate that some products contain multiple substances. Furthermore, investigative toxicology reports of drug screens in which more than one substance was detected indicate that users have ingested products composed of drug combinations (e.g., a tablet composed of MDPV and BZP) or multiple drug products (e.g., a MDPV powder product and a MDMA tablet).

Factor 5: Scope, Duration and Significance of Abuse

The popularity of synthetic cathinones as recreational drugs has increased since they first appeared on the United States' illicit drug market. According to forensic laboratory reports, the first appearance of these synthetic cathinones in the United States occurred in 2009. In 2009, NFLIS registered 15 exhibits from 8 states containing these three synthetic cathinones. In 2010, there were 574 reports from 29 states related to these substances registered in NFLIS, and in

2011 (January to August) there were 995.³

Based on reports to DEA from law enforcement and public health officials, synthetic cathinones are becoming increasingly prevalent and abused throughout the United States. At one United States point of entry, the U.S. Customs and Border Protection (CBP) has encountered at least 127 shipments containing primarily mephedrone, methylone, and MDPV, as well as other synthetic cathinones like 4-MEC, butylone, fluoromethcathinone, and dimethylcathinone. Most of these shipments originated in China or India and were being shipped to destinations throughout the United States such as Arizona, Alaska, Hawaii, Kansas, Louisiana, Oklahoma, Oregon, Pennsylvania, Missouri, Virginia, Washington, and West Virginia. The American Association of Poison Control Centers (AAPCC), a non-profit, national organization that represents the poison control centers of the United States, reported that in 2010, poison control centers took 303 calls about synthetic cathinones. However, in just the first eight months of 2011, poison control centers have already received 4,720 calls relating to these products. These calls were received in poison control centers representing at least 47 states and the District of Columbia. Individual state poison control centers have also reported an increase in the number of calls regarding "bath salts" from 2009 to 2011.

Concerns over the abuse of these and other synthetic cathinones have prompted many states to control these substances. As of September 15, 2011, at least 37 states have emergency scheduled or enacted legislation placing regulatory controls on some or many of the synthetic cathinones. These states include Alabama, Arkansas, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Michigan, Minnesota, Mississippi, Missouri, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Tennessee, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin and Wyoming. Several countries including all members of the European Union have also placed controls on the possession and/or sale of one or more of these substances. Moreover, the use of synthetic cathinones by members of the U.S. Armed Forces is prohibited.

³ Analyzed on September 15, 2011.

Factor 6: What, if Any, Risk There Is to the Public Health

The risks to the public health associated with the abuse of mephedrone, methylone, and MDPV relate to acute and long term public health and safety problems. These synthetic cathinones have become a serious drug abuse threat as there have been reports of emergency room admissions and deaths associated with the abuse of these substances.

Clinical case reports indicate that these synthetic cathinones produce a number of stimulant-like adverse effects such as palpitation, seizure, vomiting, sweating, headache, discoloration of the skin, hypertension, and hyper-reflexia. Adverse effects associated with consumption of these drugs as reported by abusers include nose-bleeds, bruxism (teeth grinding), paranoia, hot flashes, dilated pupils, blurred vision, dry mouth/thirst, palpitations, muscular tension in the jaw and limbs, headache, agitation, anxiety, tremor, and fever or sweating. Consequently, numerous individuals have presented at emergency departments in response to exposure incidents and several cases of acute toxicity have been reported due to the ingestion of mephedrone, methylone, or MDPV. In addition, case reports have shown that the abuse of synthetic cathinones can lead to psychological dependence like that reported for other stimulant drugs.

According to clinical case reports, investigative toxicological reports, and autopsy reports, mephedrone, methylone, and MDPV have been implicated in drug induced overdose deaths. In at least three reported deaths, one of these synthetic cathinones was ruled as the cause of death. Other deaths involved individuals under the influence of these synthetic cathinones who acted violently and unpredictably in causing harm to themselves or others. There have also been reports in the scientific literature of deaths caused by individuals who were driving under the influence of these synthetic cathinones.

A number of synthetic cathinones and their products, as identified by CBP and reported in the scientific literature, appear to originate from foreign sources. The manufacturers and retailers who make and sell these products do not fully disclose the product ingredients including the active ingredients or the health risks and potential hazards associated with these products. This poses significant risk to abusers who may not know what they are purchasing or the risk associated with the use of those products.

Based on the above data, the continued uncontrolled manufacture, distribution, importation, exportation, and abuse of mephedrone, methylone, and MDPV pose an imminent hazard to the public safety. DEA is not aware of any recognized therapeutic uses of these synthetic cathinones in the United States.

DEA has considered the three criteria for placing a substance into Schedule I of the CSA (21 U.S.C. 812), and finds that the data available and reviewed for mephedrone, methylone, and MDPV indicate that these synthetic cathinones each have a high potential for abuse, no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision.

In accordance with the provisions of section 201(h) of the CSA (21 U.S.C. 811(h)) and 28 CFR 0.100, the Administrator has considered the available data and the three factors required to support a determination to temporarily schedule three synthetic cathinones (4-methyl-N-methylcathinone, 3,4-methylenedioxy-N-methylcathinone, and 3,4-methylenedioxypropylvalerone) in Schedule I of the CSA and finds that placement of these synthetic cathinones and their salts, isomers, and salts of isomers into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety.

Regulatory Requirements

With the issuance of this final order, mephedrone, methylone, and MDPV become subject to the regulatory controls and administrative, civil and criminal sanctions applicable to the manufacture, distribution, possession, importation and exportation of a Schedule I controlled substance under the CSA.

1. Registration. Any person who manufactures, distributes, dispenses, imports, exports, or possesses mephedrone, methylone, or MDPV or who engages in research or conducts instructional activities with respect to mephedrone, methylone, or MDPV, or who proposes to engage in such activities, must be registered to conduct such activities in accordance with 21 U.S.C. 823 and 958. Any person who is currently engaged in any of the above activities and is not registered with DEA must submit an application for registration and may not continue their activities until DEA has approved that application. Retail sales of Schedule I controlled substances to the general public are not allowed under the Controlled Substances Act.

2. Security. Mephedrone, methylone, and MDPV are subject to Schedule I security requirements. Accordingly, appropriately registered DEA registrants must manufacture, distribute and store these substances in accordance with 1301.71; 1301.72(a), (c), and (d); 1301.73; 1301.74; 1301.75(a) and (c); and 1301.76 of Title 21 of the Code of Federal Regulations as of October 21, 2011.

3. Labeling and packaging. All labeling and packaging requirements for controlled substances set forth in Part 1302 of Title 21 of the Code of Federal Regulations shall apply to commercial containers of mephedrone, methylone, and MDPV. Current DEA registrants shall have thirty (30) calendar days from the effective date of this Final Order to be in compliance with all labeling and packaging requirements.

4. Quotas. Quotas for mephedrone, methylone, and MDPV will be established based on registrations granted and quota applications received pursuant to Part 1303 of Title 21 of the Code of Federal Regulations.

5. Inventory. Every DEA registrant who possesses any quantity of mephedrone, methylone, or MDPV is required to keep inventory of all stocks of these substances on hand pursuant to 1304.03, 1304.04, and 1304.11 of Title 21 of the Code of Federal Regulations. Every current DEA registrant who desires registration in Schedule I for mephedrone, methylone, or MDPV shall conduct an inventory of all stocks of these substances. Current DEA registrants shall have thirty (30) calendar days from the effective date of this Final Order to be in compliance with all inventory requirements.

6. Records. All registrants who handle mephedrone, methylone, or MDPV are required to keep records pursuant to 1304.03, 1304.04, 1304.21, 1304.22, and 1304.23 of Title 21 of the Code of Federal Regulations. Current DEA registrants shall have thirty (30) calendar days from the effective date of this Final Order to be in compliance with all recordkeeping requirements.

7. Reports. All registrants are required to submit reports in accordance with 1304.33 of Title 21 of the Code of Federal Regulations. Registrants who manufacture or distribute mephedrone, methylone, or MDPV are required to comply with these reporting requirements and shall do so as of October 21, 2011.

8. Order Forms. All registrants involved in the distribution of mephedrone, methylone, or MDPV must comply with order form requirements of Part 1305 of Title 21 of the Code of

Federal Regulations as of October 21, 2011.

9. Importation and Exportation. All importation and exportation of mephedrone, methylone, or MDPV must be conducted by appropriately registered DEA registrants in compliance with Part 1312 of Title 21 of the Code of Federal Regulations on or after October 21, 2011.

10. Criminal Liability. The manufacture, distribution, dispensation, or possession with the intent to conduct these activities: Possession, importation, or exportation of mephedrone, methylone, or MDPV not authorized by, or in violation of the CSA or the Controlled Substances Import and Export Act occurring as of October 21, 2011 is unlawful.

Pursuant to the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act) (5 U.S.C. 801-808), DEA has submitted a copy of this Final Order to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

Under the authority vested in the Attorney General by section 201(h) of the CSA (21 U.S.C. 811(h)), and delegated to the Administrator of the DEA by Department of Justice regulations (28 CFR 0.100), the Administrator hereby orders that 21 CFR Part 1308 be amended as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

■ 1. The authority citation for Part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

■ 2. Section 1308.11 is amended by adding new paragraphs (g)(6), (7) and (8) to read as follows:

§ 1308.11 Schedule I.

* * * * *

(g) * * *
(6) 4-methyl-N-methylcathinone—1248

(Other names: mephedrone)

(7) 3,4-methylenedioxy-N-methylcathinone—7540

(Other names: methylone)

(8) 3,4-methylenedioxypropylvalerone—7535

(Other names: MDPV)

* * * * *

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Emerging Drugs

K2/Spice

- InfoFacts: [Spice](#)
- Sara Bellum Blog: ["Spice" - Not as Fun as it Sounds](#)

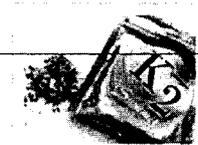


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Salvia

- InfoFacts: [Salvia](#)
- Sara Bellum Blog: [NIDA News: Back to the Future?](#)

Bath Salts

- Messages from the Director: ["Bath Salts" - Emerging and Dangerous Products](#)
- What's New at NIDA: [New findings on the active chemicals found in "bath salts" add justification to the growing health concern](#)
- What's New at NIDA: [Research sheds light on effects of mephedrone \("bath salts"\)](#)
- Sara Bellum Blog: [Keep "Bath Salts" in the Tub](#)



Additional Resources:

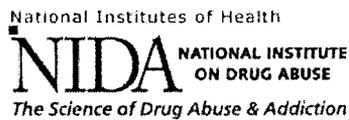
- [Commonly Abused Drugs Chart](#)
- [Monitoring the Future Survey, Overview of Findings 2011](#)
- Office of National Drug Control Policy: [Synthetic Drugs](#)

The National Institute on Drug Abuse (NIDA) is part of the National Institutes of Health (NIH), a component of the U.S. Department of Health and Human Services. **NIH...Turning Discovery Into Health**

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Questions for our staff? E-mail information@nida.nih.gov or call 301-443-1124 (240-221-4007 en español).

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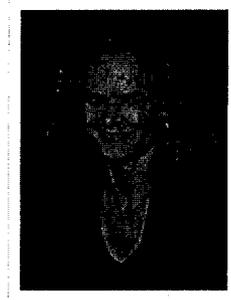


Messages From the Director

"Bath Salts" - Emerging and Dangerous Products

February 2011

"Bath Salts", the newest fad to hit the shelves (virtual and real), is the latest addition to a growing list of items that young people can obtain to get high. The synthetic powder is sold legally online and in drug paraphernalia stores under a variety of names, such as "Ivory Wave," "Purple Wave," "Red Dove," "Blue Silk," "Zoom," "Bloom," "Cloud Nine," "Ocean Snow," "Lunar Wave," "Vanilla Sky," "White Lightning," "Scarface," and "Hurricane Charlie." Because these products are relatively new to the drug abuse scene, our knowledge about their precise chemical composition and short- and long-term effects is limited, yet the information we do have is worrisome and warrants a proactive stance to understand and minimize any potential dangers to the health of the public.



We know, for example, that these products often contain various amphetamine-like chemicals, such as methylenedioxypyrovalerone (MPDV), mephedrone and pyrovalerone. These drugs are typically administered orally, by inhalation, or by injection, with the worst outcomes apparently associated with snorting or intravenous administration. Mephedrone is of particular concern because, according to the United Kingdom experience, it presents a high risk for overdose. These chemicals act in the brain like stimulant drugs (indeed they are sometimes touted as cocaine substitutes); thus they present a high abuse and addiction liability. Consistent with this notion, these products have been reported to trigger intense cravings not unlike those experienced by methamphetamine users, and clinical reports from other countries appear to corroborate their addictiveness. They can also confer a high risk for other medical adverse effects. Some of these may be linked to the fact that, beyond their known psychoactive ingredients, the contents of "bath salts" are largely unknown, which makes the practice of abusing them, by any route, that much more dangerous.

Unfortunately, "bath salts" have already been linked to an alarming number of ER visits across the country. Doctors and clinicians at U.S. poison centers have indicated that ingesting or snorting "bath salts" containing synthetic stimulants can cause chest pains, increased blood pressure, increased heart rate, agitation, hallucinations, extreme paranoia, and delusions. It is noteworthy that, even though we are barely two months into 2011, there have been 251 calls related to "bath salts" to poison control centers so far this year. This number already exceeds the 236 calls received by poison control centers for all of 2010. In response to this emerging threat, several states, including Hawaii, Michigan, Louisiana, Kentucky, and North Dakota, have introduced legislation to ban these products, which are incidentally labeled as "not fit for human consumption." In addition, several counties, cities, and local municipalities have also taken action to ban these products.

We will continue to monitor the situation and promote research on the extent, pharmacology, and consequences of "bath salts" abuse. In the meantime, I would like to urge parents, teachers, and the public at large to be aware of the potential dangers associated with the use of these drugs and to exercise a judicious level of vigilance that will help us deal with this problem most effectively.

Sincerely,

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse

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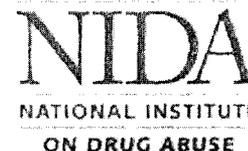
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What's New @ the National Institute on Drug Abuse

www.drugabuse.gov



JANUARY 2012

Press Releases

Cigarette and alcohol use at historic low among teens
Cigarette and alcohol use by eighth, 10th and 12th-graders are at their lowest point since the Monitoring the Future (MTF) survey began polling teenagers in 1975, according to this year's survey results. However, this positive news is tempered by a slowing rate of decline in teen smoking as well as continued high rates of abuse of other tobacco products (e.g., hookahs, small cigars, smokeless



L to R: Gil Kerlikowske and Drs. Nora Volkow, Howard Koh and Lloyd Johnston

tobacco), marijuana and prescription drugs. The survey results appeared to show that more teens continue to abuse marijuana than cigarettes; and alcohol is still the drug of choice among all three age groups queried. MTF is an annual survey of eighth, 10th, and 12th-graders conducted by researchers at the University of Michigan, Ann Arbor, under a grant from NIDA. [Read more =>](#)

News from this year's survey was announced December 14th during a press conference in Washington, D.C. NIDA Director Dr. Nora Volkow presented the survey results, and was joined by ONDCP Director Gil Kerlikowske, Assistant Secretary for Health at HHS Dr. Howard Koh, and Principal Investigator Dr. Lloyd Johnston. Media coverage of the event was extensive, reaching more than 41 million viewers. The national network placements included *ABC World News Tonight*, *CBS Evening News*, *PBS Newshour*, and *NBC Nightly News with Brian Williams*. National cable placements included *CNN Health* and several others. Locally, stories ran in all of the top 50 markets, including multiple stations in the top 10 markets. Print coverage included 375 articles, including *USA Today*, *Associated Press*, *UPI.com*, *New York Times*, *Los Angeles Times*, *Reuters*, *Washington Post*, *National Journal*, *Time*, *Education Week*, and *HealthDay*. Additionally, there were close to 300 tweets posted about the survey. [Listen to the audiocast of the press conference =>](#) | [View additional information on the MTF survey =>](#)

[back to top ↑](#)

Research News

NIDA leads pain project

The NIH Pain Consortium is encouraging medical, dental, nursing and pharmacy schools to respond to a new funding opportunity to develop Centers of Excellence in Pain Education. On December 30, 2011, a Request for Proposals (RFP) was released by Altarum Institute and Palladian Partners, an Altarum company, on behalf of the NIH Pain Consortium, to develop and disseminate pain management curriculum resources for health care professionals and provide leadership for change in pain management education. NIDA's Dr. Dave Thomas leads the project for the NIH Pain Consortium. For questions, contact [Dr. Thomas](#). [View the RFP =>](#)



New findings on the active chemicals found in "bath salts" add justification to the growing health concern

In this issue

- [Press Releases](#)
- [Research News](#)
- [Other News](#)

Upcoming Conferences and Exhibits



Community Anti-Drug Coalitions of America National Leadership Forum XXII
National Harbor, MD
February 6-9, 2012

National Science Teachers Association National Conference on Science Education
Indianapolis, IN
March 29-April 1, 2012

Blending Conference on SBIRT at American Society of Addiction Medicine Annual Meeting
Atlanta, GA
April 19-22, 2012

American Psychiatric Association Annual Meeting
Philadelphia, PA
May 5-9 2012

*For more information about these conferences, please contact [Joan Nolan](#).

Interviews



Dr. Nora Volkow was interviewed and photographed for *Washingtonian's* "100 Most Powerful Women" feature. [View the story =>](#)

Recent research by scientists at NIDA indicated that, just like MDMA (Ecstasy), the active compounds in "bath salts" — mephedrone and methylone — bind to monoamine transporters on the surface of some neurons. This in turn leads to an increase in the brain chemicals serotonin, and, to a lesser extent dopamine, suggesting a mechanism that could underlie the addictive potential of these compounds. The study was published in *Neuropsychopharmacology*. [View the article](#) ⇒

Family-centered program reduces substance use and conduct problems in rural black teens

NIDA-funded researchers have demonstrated that a family-centered program, the Strong African American Families-Teen (SAAF-T), reduces substance use, conduct problems, and symptoms of depression among black adolescents in a geographically rural area by more than 30% (compared to adolescents in a control condition) across nearly two years. [View the article published in *Pediatrics*](#) ⇒

Communities That Care program to prevent drug use makes good use of public dollars, analysis shows

A recent analysis by HHS-funded researchers showed that the Communities That Care (CTC) prevention program, a public health initiative aimed at reducing risky teen behaviors such as drug use, garners a positive return on investment that increases with time. According to the cost-benefit analysis, CTC programs showed \$5 - \$10 in returns for every \$1 invested. Benefits stemmed from anticipated reductions in smoking-related mortality, improved health, lower medical expenses, and, mainly, from lower criminal justice system and crime victimization costs over the life course of program participants. [View the article published in *Prevention Science*](#) ⇒

New targets for medications hold promise for pain relief without side effects, two studies in mice show

Two NIDA-funded articles described new potential targets for the treatment of pain without significant side effects that limited their use, including the possibility of addiction. One study was published in the *Proceedings of the National Academy of Sciences* and the other study was published in *Nature Neuroscience*. [View the *Proceedings of the National Academy of Sciences* study](#) ⇒ | [View the *Nature Neuroscience* study](#) ⇒

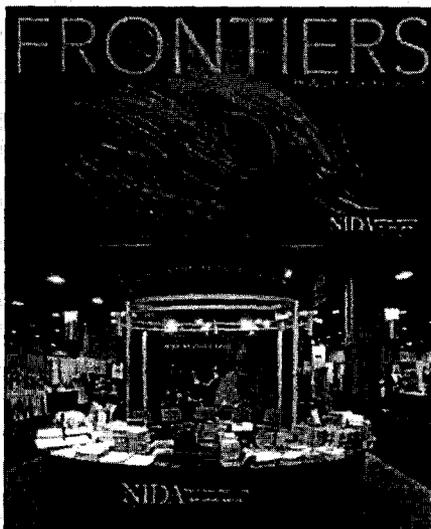
NOTE: If you cannot access a journal article, please check [PubMed Central \(PMC\)](#), the free, digital NIH archive of biomedical and life sciences journal literature.

[back to top](#) ↑

Other News

Society for Neuroscience (SfN) Meeting

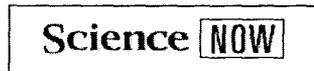
NIDA staff attended and exhibited at the annual [Society for Neuroscience Convention](#) in Washington, D.C. in November. Highlights from the convention included presentations on *Autism, Addiction and MeCP2, Synapse Organization and Plasticity in Drug Addiction, Using Optogenetic Tools to Shed Light on the Neural Mechanisms of Addiction and the Neurobiology of Behavioral and Emotional Regulation/Dysregulation*. In addition, NIDA's press team, along with the [Addiction Studies Program](#), arranged a journalist workshop during the SfN Mini-Convention. This included a Q&A with Dr. Volkow, with over 30 reporters in attendance. Dr. Volkow was also interviewed by several media outlets at SfN, including [Wall Street Journal](#), [Addiction Inbox](#), and [Houston Chronicle](#). Video interviews conducted with NIDA grantees and staff at the NIDA Mini-convention will appear on NIDA's web and YouTube sites in early 2012.



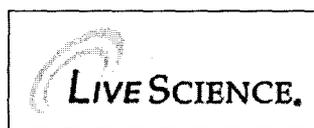
NIDA grantee Dr. David Jentsch receives Jacob P. Waletzky Memorial Award



Discover Magazine interviewed IRP researcher Dr. Zheng-Xiong Xi about the role that the endocannabinoid system plays in drug craving. [View the story](#) ⇒



Dr. Wilson Compton was included in a story about atmospheric concentrations of addictive drugs. [View the story](#) ⇒



IRP researcher Dr. Michael Baumann spoke to *Live Science* about designer drugs, including mephedrone and methylone. [View the story](#) ⇒



Dr. Compton was interviewed about the DSM-5. [View the story \(after logging in.\)](#) ⇒

Dr. Compton also participated in a virtual discussion with other psychiatrists regarding prescription drug abuse. [View discussion](#) ⇒

General Information

For more information about NIDA e-mail information@nida.nih.gov

For press inquiries e-mail media@nida.nih.gov

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Connect with NIDA



Dr. Volkow recognized NIDA grantee Dr. David Jentsch as the recipient of the 2011 Jacob P. Waletzky Memorial Award during the SfN Convention. Dr. Jentsch won for his studies on the genetic and neurochemical determinants of cognitive and executive functions, the mechanisms of action of psychotherapeutic drugs, novel strategies for modulating cognitive deficits in schizophrenia, addiction and ADHD, and animal models of psychiatric disorders. Established in 2003 by the Waletzky family, the SfN Jacob P. Waletzky Memorial Award is given to a young scientist (within 15 years of receiving a doctoral degree) for innovative research in substance abuse.



National High School Journalist Convention

NIDA planned and participated in a two-hour prescription drug abuse panel during the



National High School Journalism Convention held November 18th in Minneapolis, MN. OSP's Stephanie Older and Jen Elcano, and NIDA grantee Dr. Carol Boyd were panelists, and presented the latest scientific research and trends related to prescription drug abuse and NIDA's resources for journalists. Over 50 student journalists and journalism advisors attended. NIDA's press team also produced ads for the convention program and teacher/advisor registration bags to reach the 4,500 students and 800 publications advisors at the convention, which is sponsored by the Journalism Education Association (JEA) and the National Scholastic Press Association (NSPA).

NIDA Commemorates World AIDS Day

On November 8th, the NIH hosted Secretary of State Hillary Rodham Clinton as she presented a vision for "Creating an AIDS-Free Generation," calling for a combination of proven strategies — including HIV treatment as HIV prevention — to achieve this worthy goal. In honor of World AIDS Day, Dr. Volkow distributed a Message from the Director highlighting Secretary of State Hillary Rodham Clinton's vision. Also, each year, NIDA displays several panels from the AIDS Memorial Quilt in the Neuroscience Center lobby.



AIDS Memorial Quilt

NIDA's Dr. Jag Khalsa attends CSAM Annual Conference

Dr. Jag Khalsa, Chief, Medical Consequences Branch at NIDA and Dr. Marc Ware, a physician from Montreal, participated in a debate about the merits of both inhaled and pharmacological THC preparations at the Canadian Society of Addiction Medicine's Annual Conference on November 4-6, 2011 in Vancouver, Canada. Dr. Paul Sobey moderated the debate.



From L to R: Drs. Paul Sobey, Jag Khalsa and Marc Ware

Dr. Petra Jacobs Delivers Greetings to Addiction Training Institute

Dr. Petra Jacobs, Assistant Director of NIDA's Center for the Clinical Trials Network, delivered pre-recorded greetings on October 8th and 22nd to participants of the Addiction Training Institute in Prague, the Czech Republic. Dr. Jacobs congratulated the Institute founders, PhDr. Magdalena Frouzova and Prof. Jiri Heller, on the twenty year anniversary of starting the first systematic training on the psychotherapy of drug addiction. This Training Institute is one of the key Czech Institutes to guide professional development of clinicians and specialists working with patients with substance abuse and other mental illnesses.



L to R: PhDr. Magdalena Frouzova and Dr. Petra Jacobs

IRP's Dr. Yavin Shaham appointed Senior Editor of Journal of Neuroscience

NIDA IRP's Dr. Yavin Shaham was recently appointed Senior Editor for the Journal of Neuroscience, covering issues on Behavioral/Systems/Cognitive Neuroscience. Congratulations Yavin!



Drs. Michael Dennis and Christy Scott earn Hazelden's Dan Anderson Research Award

Two NIDA grantees, Michael L. Dennis, Ph.D., Senior Research Psychologist at the Lighthouse Institute, Chestnut Health Systems, and Christy K. Scott, Ph.D., Research Psychologist at the Lighthouse Institute, have both earned the latest Dan Anderson Research Award for their long-term outcomes study examining the effectiveness of Recovery Management Checkups on treatment outcomes among adults



attending alcohol/drug treatment. Sponsored by the Butler Center for Research at Hazelden, the award honors a single published article by a researcher who has advanced the scientific knowledge of addiction treatment and recovery.

Drs. Dennis and Scott earned the award for their study, "Four-year outcomes from the Early Re-Intervention (ERI) experiment using Recovery Management Checkups (RMCs)," soon to be published in an upcoming print issue of *Drug and Alcohol Dependence*. Drs. Dennis and Scott will accept the award this coming spring at the National Association of Addiction Treatment Providers (NAATP) annual conference in Phoenix.

[back to top](#) ↑



The National Institute on Drug Abuse (NIDA) is part of the National Institutes of Health (NIH), the principal biomedical and behavioral research agency of the United States Government. NIH is a component of the U.S. Department of Health and Human Services.

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Original Article

Neuropsychopharmacology, (14 December 2011) |
doi:10.1038/npp.2011.304

The Designer Methcathinone Analogs, Mephedrone and Methylone, are Substrates for Monoamine Transporters in Brain Tissue

Michael H Baumann, Mario A Ayestas, John S Partilla, Jacqueline R Sink, Alexander T Shulgin, Paul F Daley, Simon D Brandt, Richard B Rothman, Arnold E Ruoho and Nicholas V Cozzi

The nonmedical use of ‘designer’ cathinone analogs, such as 4-methylmethcathinone (mephedrone) and 3,4-methylenedioxymethcathinone (methylone), is increasing worldwide, yet little information is available regarding the mechanism of action for these drugs. Here, we employed in vitro and in vivo methods to compare neurobiological effects of mephedrone and methylone with those produced by the structurally related compounds, 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine. In vitro release assays using rat brain synaptosomes revealed that mephedrone and methylone are nonselective substrates for plasma membrane monoamine transporters, similar to MDMA in potency and selectivity. In vivo microdialysis in rat nucleus accumbens showed that i.v. administration of 0.3 and 1.0 mg/kg of mephedrone or methylone produces dose-related increases in extracellular dopamine and serotonin (5-

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- › Michael H Baumann
- › Mario A Ayestas
- › John S Partilla
- › Jacqueline R Sink
- › Alexander T Shulgin
- › Paul F Daley
- › more authors of this article

HT), with the magnitude of effect on 5-HT being greater. Both methcathinone analogs were weak motor stimulants when compared with methamphetamine. Repeated administrations of mephedrone or methylone (3.0 and 10.0 mg/kg, s.c., 3 doses) caused hyperthermia but no long-term change in cortical or striatal amines, whereas similar treatment with MDMA (2.5 and 7.5 mg/kg, s.c., 3 doses) evoked robust hyperthermia and persistent depletion of cortical and striatal 5-HT. Our data demonstrate that designer methcathinone analogs are substrates for monoamine transporters, with a profile of transmitter-releasing activity comparable to MDMA. Dopaminergic effects of mephedrone and methylone may contribute to their addictive potential, but this hypothesis awaits confirmation. Given the widespread use of mephedrone and methylone, determining the consequences of repeated drug exposure warrants further study.

partner of AGORA, HINARI, OARE, INASP, ORCID, CrossRef and COUNTER

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Neuropsychopharmacology ISSN 0893-133X EISSN 1470-634X

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60



Re: status reports 
Evelyn Soo to: Nathan Isotalo

2012-03-09 10:06 AM

History: This message has been replied to.

Absolutely!

~~This was done way before my time but it has to be approved before status information is released.~~

Thanks
Evelyn

Evelyn C Soo, PhD
A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
environnementale et de la sécurité des consommateurs (DGSESC)
Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
evelyn.soo@hc-sc.gc.ca
Telephone | Téléphone 613-954-1758
Government of Canada | Gouvernement du Canada

Nathan Isotalo Hi Evelyn, was the MDPV status report ever ap... 2012-03-08 03:13:04 PM

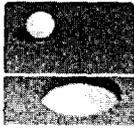
From: Nathan Isotalo/HC-SC/GC/CA
To: Evelyn Soo/HC-SC/GC/CA@HWC
Date: 2012-03-08 03:13 PM
Subject: Re: status reports

Hi Evelyn,

was the MDPV status report ever approved? Nathan.

Evelyn Soo Here you are. Let me know if you have any ques... 2012-03-08 03:00:03 PM
Nathan Isotalo Hi Evelyn could you please provide the status re... 2012-03-08 02:57:53 PM

61



Re: re methylone 
Evelyn Soo to: Nathan Isotalo
Cc: Status

2012-03-09 11:56 AM

History: This message has been replied to and forwarded.

Hi Nathan

Yes, status is CONTROLLED under item 1 of Schedule III to the CDSA.

Evelyn

Evelyn C Soo, PhD
A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
environnementale et de la sécurité des consommateurs (DGSESC)
Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
evelyn.soo@hc-sc.gc.ca
Telephone | Téléphone 613-954-1758
Government of Canada | Gouvernement du Canada

Nathan Isotalo Good morning, Evelyn do you have a status dec...

2012-03-09 11:22:02 AM

From: Nathan Isotalo/HC-SC/GC/CA
To: Evelyn Soo/HC-SC/GC/CA@HWC
Date: 2012-03-09 11:22 AM
Subject: re methylone

Good morning, Evelyn

do you have a status decision on "methylone"? I suspect that it would be an Sch. III analogue of
cathinone. Chem name: 3,4-methylenedioxy-N-methylcathinone.

thank you. Nathan.

62



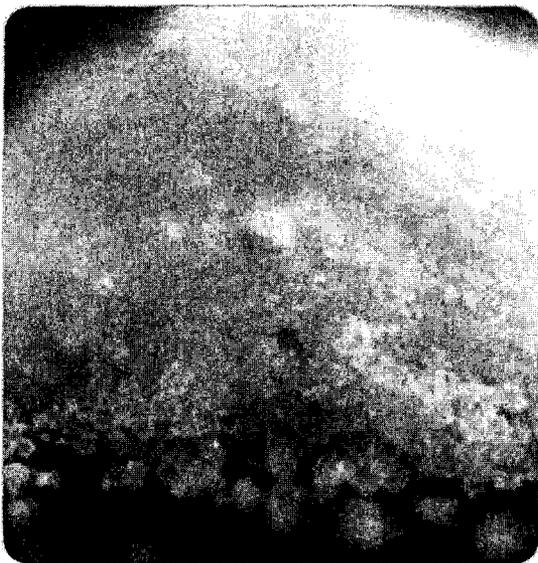
XII. Drugs of Concern

Even though some substances are not currently controlled by the Controlled Substances Act, they pose risks to individuals who abuse them. The following section describes these drugs of concern and their associated risks.

Bath Salts or Designer Cathinones (*Synthetic Stimulants*)

WHAT ARE "BATH SALTS?"

Synthetic stimulants that are marketed as "bath salts" are often found in a number of retail products. These synthetic stimulants are chemicals. The chemicals are synthetic derivatives of cathinone, a central nervous system stimulant, which is an active chemical found naturally in the khat plant. Mephedrone and MDPV (3-4 methylenedioxypyrovalerone) are two of the designer cathinones most commonly found in these "bath salt" products. Many of these products are sold over the Internet, in convenience stores, and in "head shops."



Bath salts

WHAT IS THEIR ORIGIN?

Law enforcement officials believe that the stimulant chemicals contained in these products are manufactured in China and India and packaged for wholesale distribution in Eastern Europe. Many countries have banned these products.

What are common street names?

→ Bilss, Blue Silk, Cloud Nine, Drone, Energy-1, Ivory Wave, Lunar Wave, Meow Meow, Ocean Burst, Pure Ivory, Purple Wave, Red Dove, Snow Leopard, Stardust, Vanilla Sky, White Dove, White Knight, White Lightening

What does it look like?

"Bath salt" stimulant products are sold in powder form in small plastic or foil packages of 200 and 500 milligrams under various brand names. Mephedrone is a fine white, off-white, or slightly yellow-colored powder. It can also be found in tablet and capsule form. MDPV is a fine white or off-white powder.

How is it abused?

"Bath salts" are usually ingested by sniffing/snorting. They can also be taken orally, smoked, or put into a solution and injected into veins.

What is their effect on the mind?

People who abuse these substances have reported agitation, insomnia, irritability, dizziness, depression, paranoia, delusions, suicidal thoughts, seizures, and panic attacks. Users have also reported effects including impaired perception of reality, reduced motor control, and decreased ability to think clearly.

What is their effect on the body?

Cathinone derivatives act as central nervous system stimulants causing rapid heart rate (which may lead to heart attacks and strokes), chest pains, nosebleeds, sweating, nausea, and vomiting.

What are their overdose effects?

These substances are usually marketed with the warning "not intended for human consumption." Any time that users put uncontrolled or unregulated substances into their bodies, the effects are unknown and can be dangerous.

Which drugs cause similar effects?

→ Amphetamine, Cocaine, Khat, LSD, MDMA

What is their legal status in the United States?

Mephedrone has no approved medical use in the United States. It is not specifically scheduled under the Controlled Substances Act, but it is a chemical analogue of methcathinone, which is a Schedule I controlled substance. Incidents involving mephedrone can be prosecuted under the Federal Analog Act of the Controlled Substances Act. MDPV (3,4-methylenedioxypropylrovalerone) has no approved medical use in the United States. MDPV is not scheduled under the CSA.

63



Drug Fact Sheet

Bath Salts or Designer Cathinones (Synthetic Stimulants)

Overview

Synthetic stimulants that are marketed as "bath salts" are often found in a number of retail products. These synthetic stimulants are chemicals. The chemicals are synthetic derivatives of cathinone, a central nervous system stimulant, which is an active chemical found naturally in the khat plant. Mephedrone and MDPV (3,4-methylenedioxypyrovalerone) are two of the designer cathinones most commonly found in these "bath salt" products. Many of these products are sold over the Internet, in convenience stores, and in "head shops."

Street names

Bilss, Blue Silk, Cloud Nine, Drone, Energy-1, Ivory Wave, Lunar Wave, Meow Meow, Ocean Burst, Pure Ivory, Purple Wave, Red Dove, Snow Leopard, Stardust, Vanilla Sky, White Dove, White Knight, White Lightening

Looks like

"Bath salt" stimulant products are sold in powder form in small plastic or foil packages of 200 and 500 milligrams under various brand names. Mephedrone is a fine white, off-white, or slightly yellow-colored powder. It can also be found in tablet and capsule form. MDPV is a fine white or off-white powder.

Methods of abuse

"Bath salts" are usually ingested by sniffing/snorting. They can also be taken orally, smoked, or put into a solution and injected into veins.

Affect on mind

People who abuse these substances have reported agitation, insomnia, irritability, dizziness, depression, paranoia, delusions, suicidal thoughts, seizures, and panic attacks. Users have also reported effects including impaired perception of reality, reduced motor control, and decreased ability to think clearly.

Affect on body

Cathinone derivatives act as central nervous system stimulants causing rapid heart rate (which may lead to heart attacks and strokes), chest pains, nosebleeds, sweating, nausea, and vomiting.

Drugs causing similar effects

Drugs that have similar effects include: amphetamines, cocaine, Khat, LSD, and MDMA.

Overdose effects

These substances are usually marketed with the warning "not intended for human consumption." Any time that users put uncontrolled or unregulated substances into their bodies, the effects are unknown and can be dangerous.

Legal status in the United States

On Friday, October 21, 2011, DEA published a final order in the Federal Register exercising its emergency scheduling authority to control three synthetic stimulants that are used to make bath salts, including: Mephedrone, 3,4-methylenedioxypyrovalerone (MDPV) and Methyllone. Except as authorized by law, this action makes possessing and selling these chemicals, or the products that contain them, illegal in the United States. This emergency action was necessary to prevent an imminent threat to the public safety. The temporary scheduling action will remain in effect for at least one year while the DEA and the United States Department of Health and Human Services (DHHS) further study whether these chemicals should be permanently controlled. As a result of this order, these synthetic stimulants are designated as Schedule I substances under the Controlled Substances Act. Schedule I status is reserved for those substances with a high potential for abuse, no currently accepted use for treatment in the United States and a lack of accepted safety for use of the drug under medical supervision.

64

The Toxicology of Bath Salts: A Review of Synthetic Cathinones

Jane M. Prosser · Lewis S. Nelson

Published online: 23 November 2011
© American College of Medical Toxicology 2011

Abstract Synthetic cathinones have recently emerged and grown to be popular drugs of abuse. Their dramatic increase has resulted in part from sensationalized media attention as well as widespread availability on the Internet. They are often considered “legal highs” and sold as “bath salts” or “plant food” and labeled “not for human consumption” to circumvent drug abuse legislation. Cathinone is a naturally occurring beta-ketone amphetamine analogue found in the leaves of the *Catha edulis* plant. Synthetic cathinones are derivatives of this compound. Those that are being used as drugs of abuse include butylone, dimethylcathinone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, mephedrone, methedrone, methylenedioxypropylone (MDPV), methylone, and pyrovalerone. Synthetic cathinones are phenylalkylamines derivatives, and are often termed “bk-amphetamines” for the beta-ketone moiety. They may possess both amphetamine-like properties and the ability to modulate serotonin, causing distinct psychoactive effects. Desired effects reported by users of synthetic cathinones include increased energy, empathy, openness, and increased libido. Cardiac, psychiatric, and neurological signs and symptoms are the most common adverse effects reported in synthetic cathinone users who require medical care. Deaths associated with use of these compounds have been reported. Exposure to and use of synthetic cathinones are becoming increasingly popular despite a lack of scientific research and understanding of

the potential harms of these substances. The clinical similarities to amphetamines and MDMA specifically are predictable based on the chemical structure of this class of agents. More work is necessary to understand the mechanisms of action, toxicokinetics, toxicodynamics, metabolism, clinical and psychological effects as well as the potential for addiction and withdrawal of these agents.

Keywords Cathinone · Mephedrone · Methedrone · MDPV · Methylone · Bath salts

Background

Synthetic cathinones have recently emerged and grown to be popular drugs of abuse. Their dramatic increase has resulted in part from sensationalized media attention as well as widespread availability. They are often considered “legal highs” and sold as “bath salts” or “plant food” and labeled “not for human consumption” to circumvent drug abuse legislation. They can be obtained through “head shops,” Internet websites, and local drug suppliers.

The legal status is variable by jurisdiction and rapidly changing, however they were initially legal in the UK and Europe. “Legal high” is a term often used to refer to drugs that are considered by users to fall outside of drug regulatory laws. They are generally labeled “not for human consumption” to subvert regulatory control. Prior to 2009, the UK Poisons Information Service had no telephone inquiries related to synthetic cathinones. However over a 1-year period from 2009 to 2010, the number of inquiries regarding synthetic cathinone derivatives equaled the number of calls about cocaine and MDMA [1]. Google Insights, a web application that tracks search terms, shows almost no searches for mephedrone before 2008. There has

J. M. Prosser (✉)
Weill Cornell Medical Center,
New York, NY, USA
e-mail: jprosser100@gmail.com

L. S. Nelson
New York University School of Medicine,
New York City Poison Control Center,
New York, NY, USA

since been a remarkable rise in the number of searches, peaking in 2009, with the highest number of searches originating from the UK [2]. For a comprehensive review of existing data, Pubmed, Medline, Google, Google Scholar were searched using the following terms: bath salts, butylone, club drugs, dimethylcathinone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, mephedrone, methedrone, methylenedioxypyrovalerone (MDPV), methylone, plant food and pyrovalerone.

Cathinone ((*S*)-2-amino-1-phenyl-1-propanone) is a naturally occurring beta-ketone amphetamine analogue found in the leaves of the *Catha edulis* (Khat) plant. Chewing the leaves of this plant for stimulant effects is popular in certain Middle Eastern countries, particularly Yemen [3]. Cathinone is found in the leaves of the plants only when fresh, and for this reason leaves can be chewed for only a few days after harvesting. Cathinone causes amphetamine-like sympathomimetic effects, including tachycardia and hypertension as well as psychoactive effects euphoria and increased alertness. Khat chewing has been linked to increased risk of myocardial infarction, dilated cardiomyopathy, and duodenal ulcers [3].

Synthesis of cathinone derivatives has been reported since the late 1920s. Methcathinone was synthesized in 1928 and mephedrone in 1929 [4, 5]. A few of these derivatives have been investigated for medical use. Currently, bupropion is the only cathinone derivative that carries a medical indication in the US and Europe. It is a ring-substituted cathinone, prescribed for the treatment of depression and for use as a smoking-cessation aid [6]. Others have been investigated, but were ultimately unsuccessful due to severe side effect profiles. Methcathinone was used in Russia as an antidepressant in the 1930s and 1940s. Also known as “Cat” and “Jeff,” it has been used recreationally most often in countries formerly part of the Soviet Union, but also gained popularity in the United States, particularly in Michigan, in the 1990s [7]. Another derivative, pyrovalerone was investigated for use as a prescription drug to treat chronic fatigue, lethargy, and obesity but was withdrawn due to abuse and dependency in users [8–10].

Numerous synthetic cathinone derivatives have become popular for use as “legal highs.” Exactly when these derivatives gained popularity amongst club goers and others seeking new drugs of abuse is difficult to pinpoint, but mentions in Internet drug forums began in 2007 [11]. Synthetic cathinones that have been found in these products include butylone, dimethylcathinone, ethcathinone, ethylone, 3 and 4-fluoromethcathinone, mephedrone, methedrone, MDPV, methylone, and pyrovalerone (see Table 1 [6, 12–14]).

Interest in synthetic cathinones as drugs of abuse developed in part due to decreased availability and purity of the

Table 1 Synthetic cathinones used as drugs of abuse with chemical names and structures

Common Name	Chemical Name	Chemical Structure
Butylone	1-(1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one	
Dimethylcathinone	(<i>RS</i>)-2-dimethylamino-1-phenylpropan-1-one	
Ethcathinone	(<i>RS</i>)-2-ethylamino-1-phenylpropan-1-one	
Ethylone	(<i>RS</i>)-1-(1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one	
3-Fluoromethcathinone	(<i>RS</i>)-1-(3-fluorophenyl)-2-methylamino propan-1-one	
4-Fluoromethcathinone	(<i>RS</i>)-1-(4-fluorophenyl)-2-methylamino propan-1-one	
Mephedrone	(<i>RS</i>)-2-methylamino-1-(4-methylphenyl)propan-1-one	
Methcathinone	α -methylamino-propio-phenone	
Methedrone	(<i>RS</i>)-1-(4-methoxyphenyl)-2-(methylamino)propan-1-one	
Methylenedioxypyrovalerone (MDPV)	(<i>RS</i>)-1-(Benzo[<i>d</i>][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one	
Methylone	(\pm)-2-methylamino-1-(3,4-methylenedioxyphe-nyl)propan-1-one	
Pyrovalerone	(<i>RS</i>)-1-(4-methylphenyl)-2-(1-pyrrolidinyl)pentan-1-one	

more typical abusable drugs. In 2009, police reports from the UK, showed a marked decrease in purity of cocaine from over 60% to 22%, which was attributed to an increased number of

drug seizures [15]. In the Netherlands, a change in the composition of tablets reported to contain MDMA was noted over a similar time period. Prior to 2009, analysis of “Ecstasy” tablets found that >90% contained MDMA, although in later samples fewer than half contained any of this substance. In these latter analyses, piperazine derivatives and mephedrone replaced MDMA [16].

Prevalence

As with many drugs of abuse, the prevalence of synthetic cathinone use is difficult to measure. Self-reported use from user surveys provides most of the currently available prevalence data. An online survey of club-goers in the UK found that 41% had used methedrone and 10% had used methylone. A third had used methedrone in the last month and 14% reported weekly use [17]. High school and college students in the UK asked to self report revealed that 20% had used mephedrone on at least one occasion, 4% reported daily use, and all of those using daily were under 21 years of age [18].

A study from Ireland analyzing urine collected from attendees at a methadone maintenance clinic found that 14% were positive for mephedrone and 3% were positive for methylone [19].

A Finnish study which analyzed blood from drivers suspected by police to be driving under the influence of drugs found that 286 of 3,000 specimens submitted for analysis contained MDPV (8.6%). Two hundred eight of these drivers underwent psycho-physical achievement deficiency testing (such as walking in a straight line and speaking without slurred speech) as an indirect measure of driving impairment. Of these, 84% were functionally impaired, with 7% of these classified as severely impaired. Many users had multiple substances identified on blood analysis, including benzodiazepines, other amphetamines, tetrahydrocannabinol, and ethanol, so impairment cannot be attributed solely to MDPV in this series [10].

In the United States, data on prevalence and use is extremely limited. The American Association of Poison Control Centers reports 303 calls related to “bath salts” in 2010. As of May 2011, 2,371 calls have already been recorded [20].

Contents

Contributing to the complexity of understanding the prevalence of use of these drugs is the difficulty in determining the exact nature of the exposure. The true contents of the product can be obscured as advertising and packaging of these products is often misleading. “Bath

salts” sold on websites reporting benign active ingredients, such as amino acids, phosphates, and magnesium salts, were found to contain synthetic cathinones [21]. Alternatively, other products advertised as containing synthetic cathinones as the active ingredients actually contained caffeine and local anesthetics [22]. Products advertising “legal highs” have been found to contain scheduled ingredients. In the UK in April 2010, mephedrone and several other cathinone derivatives were listed as class B drugs after changes were made to the Misuse of Drugs Act [23] (under UK law, drugs are classified in three categories based on danger of use and corresponding severity of legal consequences. Class A drugs are considered the most dangerous and carry the harshest penalties). Naphyrone, another derivative, remained legal until additional changes were enacted in July 2010. A study conducted in the interim period (April through July) investigated the ingredients of substances advertised online as legal for purchase because they contained the still unclassified naphyrone. Despite the assurances, these products contained controlled synthetic cathinones, placing users at legal as well as medical risk. Consistency of ingredients is also unpredictable. “Legal high” brand name products, analyzed over a 6-month period, changed ingredients in 25% of the samples [24].

Mephedrone users report obtaining the drugs from both Internet sources and local dealers. The number of users who purchased from dealers increased significantly after regulatory measures restricting possession, sale, and manufacture of synthetic cathinones passed in the UK [18, 25]. Synthetic cathinones can be purchased as powder or in pill or capsule form. UK specimens submitted to forensic providers were in powder form 95% of the time [26]. The cost of 1 g of mephedrone was approximately £16 (\$25) in the UK, increasing with the change in legal status from approximately £10 prior to regulation [25]. In the US, 1 g costs approximately \$20–35 in head shops or through the Internet [13].

Patterns of Use

The synthetic cathinones are most commonly nasally insufflated or ingested [1, 27]. “Bombing” is a method of ingestion whereby mephedrone powder is wrapped in cigarette paper and swallowed [28]. “Keying” is the practice of dipping a key into powder and then insufflating. There are approximately five to eight “keys” per gram [6]. Rectal administration, gingival delivery, inhalation, and intramuscular or intravenous injection have also been described [11, 28]. Additionally, multiple concomitant routes of administration are reported [1, 17, 27, 29]. Self-reported doses range from a few milligrams to over 1 g of

powder [6, 17, 25, 27]. Users cannot be certain of the actual contents or the purity of the drug, therefore actual exposure is highly variable [22, 24].

Mephedrone users report the onset of psychoactive effects after insufflation to be 10–20 min with an expected duration of effect of about 1–2 h; onset after oral ingestion is approximately 15–45 min with duration of 2–4 h. Intravenous users report symptoms peaking at 10–15 min with a 30 min duration of desired effects [26, 28].

Subjective User Effects

Desired effects reported by users of synthetic cathinones include increased energy, empathy, openness, and increased libido [17, 30].

Approximately 20% of users surveyed report having had an adverse effect from use of mephedrone [18, 27]. Users report increased sweating, palpitations, nausea and vomiting, headache, muscle twitching, dizziness, vertigo, or short-term memory difficulty (see Table 2).

When asked to compare mephedrone use to cocaine 60–75% reported a longer duration of effect and 50% reported a “better” effect with the former. More than 50% believed it was less addictive than cocaine. Half thought mephedrone use was equally as risky as cocaine use, with 25% feeling it was less safe and another 25% safer [17, 28].

Polysubstance abuse, both simultaneous use and on different occasions, is very common among those taking synthetic cathinones. Alcohol, tobacco, MDMA, cannabis, and cocaine were also reported by >80% of respondents surveyed about mephedrone use, in addition to an extensive list of other drugs of abuse [17]. All emergency department patients in one series presenting after reported methedrone

use had also used other drugs [31]. Urine drug screening in another series found that 16 of 17 specimens were positive for other drugs of abuse [13]. Postmortem toxicology testing has also revealed that concurrent use of other substances is common [32–34]

Adverse Clinical Effects of Synthetic Cathinones

Cardiac, psychiatric, and neurological signs and symptoms are the most common adverse effects reported in synthetic cathinone users who require medical care. There are four series detailing clinical effects of cathinones. In all, the single most common symptom was agitation ranging from mild agitation to severe psychosis requiring chemical restraint. Retrospective data from the UK Poisons information service, detailing telephone caller and internet reports of presumed cathinone exposures, noted that 28% of cases had agitation and aggression [1]. A clinical series of 72 patients who presented to a London emergency department found that 39% were agitated. Nine of the patients in this series had laboratory confirmation of mephedrone ingestion [30]. In a retrospective review of self-reported exposures in a Scottish emergency department agitation was the most common symptom [35]. Similarly, in a prospective US series 66% were agitated [13]. Cardiovascular complications were also very common, and as a group were the most common complications seen in users presenting for medical care. See Table 3 for a comparison of the clinical effects found in these four review articles.

Table 4 provides a more detailed look at specific signs and symptoms reported in the literature by health care providers about patients with reported use of these products.

Table 2 User reported clinical effects of synthetic cathinones [17, 25, 28, 30, 62]

Cardiovascular	Palpitations, shortness of breath, chest pain
ENT	Dry mouth, epistaxis, nasal pain, “nose burns”, oropharyngeal pain, tinnitus
Gastrointestinal	Abdominal pain, anorexia, nausea, vomiting
Genitourinary	Anorgasmia, erectile dysfunction, increased libido
Musculoskeletal	Arthralgias, extremity changes—coldness, discoloration, numbness, tingling, muscular tension and cramping
Neurologic	Aggressiveness, bruxism, dizziness, headache, lightheadness, memory loss, tremor, seizures
Ophthalmologic	Blurred vision, mydriasis, nystagmus
Pulmonary	Shortness of breath
Psychological	Anger, anxiety, auditory and visual hallucinations, depression, dysphoria, empathy, euphoria, fatigue, formication, increased energy, increased and decreased concentration, loquaciousness, panic, paranoia, perceptual distortions, restlessness
Other	Body odor “mephedrone stink”, diaphoresis, fever, insomnia, nightmares, skin rash

These are self-reported symptoms by users of synthetic cathinones. It is possible that these effects are not all related to cathinone use as many users take these substances simultaneously with other drugs and ethanol. Additionally due to lack of reliability and consistency of products, users may not be aware of what drug they have actually taken. Please see text for more information

Table 3 Adverse effects reported by healthcare providers from patients seeking medical care after synthetic cathinone use

	James [1]	MMWR [13]	Regan [35]	EMCDDA [30]	Total
# patients	149	35	57	72	313
Cardiac	113	30	26	63	293
Psychiatric	84	44	37	28	193
Neurologic	56	18	26	9	109
Gastrointestinal	27	NA	3	10	40
Pulmonary	13	NA	10	NA	23
Ear, nose and throat	7	NA	7	NA	14
Other	48	NA	8	NA	56

It is possible that these effects are not all related to cathinone use. Only a few of these cases were analytically confirmed as synthetic cathinone exposures. Additionally, many other substances such as ethanol and other drugs of abuse were reported or found on drug screening

Hyponatremia is a well-reported complication of MDMA use. It is thought to result from several factors including overhydration with water in the setting of drug-induced secretion of vasopressin [36]. It is unclear if synthetic cathinones cause similar changes in sodium and water regulation. There are three cases of hyponatremia reported after synthetic cathinone exposure, raising the possibility that similarities may exist. In all three cases mephedrone exposure was confirmed and no MDMA was found on body fluid analysis in these patients. A 14-year-old girl who consumed ethanol and a white powder presented with an altered mental status and Glasgow coma score of 11. She had hyponatremia 118 mmol/L and elevated intracranial pressure, and a brain MRI showing subcortical white matter changes. Her neurologic symptoms

improved with correction of the sodium except for mild dysphasia and anterograde amnesia. Two months later, she had complete resolution of all symptoms [37]. The other two cases were both fatalities. A 29-year-old British man presented to the emergency department with a fluctuating level of consciousness, hyponatremia 125 mmol/L, and was found to have cerebral edema with impending tonsillar herniation on head computed tomography. He died after care was withdrawn due to brain death [38]. An 18-year-old woman who used cannabis and mephedrone sustained a cardiac arrest. She was resuscitated, found to have hyponatremia 120 mmol/L and cerebral edema, but was declared brain dead 36 h after presentation [39].

Treatment

Treatment for patients with exposure to synthetic cathinones is primarily supportive. At this time, limited information is available to guide treatment. Benzodiazepines have been used for sedation for agitation and seizures. Given the similarities to amphetamines and cocaine, it seems likely that similar management strategies would be useful. Patients showing signs of the sympathomimetic toxidrome including agitation, psychosis, significant tachycardia, hypertension, and seizures should be treated with benzodiazepines to counteract excessive epinephrine and norepinephrine release and reuptake inhibition. Hyperthermia should be treated with aggressive cooling. Treatment of hyponatremia due to synthetic cathinones is not well described; MDMA-induced hyponatremia is treated with water restriction or hypertonic saline. Management should be directed by the severity of symptoms, and patients may benefit from an approach similar to that of MDMA-induced

Table 4 Medical provider (including emergency department and poison center data) reported effects associated with use of synthetic cathinones [1, 13, 30, 35, 38, 70–72]

Cardiovascular	Chest pain, hypertension, palpitations, myocarditis, tachycardia
ENT	Epistaxis, oral and pharyngeal effects, tongue disorder
Gastrointestinal	Abdominal pain, abnormal liver function tests, nausea, liver failure
Musculoskeletal	Elevated creatinine kinase, peripheral vasoconstriction, rhabdomyolysis
Neurologic	Agitation, aggression, altered mental status, collapse, confusion, dizziness, drowsiness, dystonia, headache, hyperreflexia, myoclonus, paraesthesias, seizures, tremor
Ophthalmologic	Abnormal vision, mydriasis
Pulmonary	Shortness of breath, tachypnea
Psychological	Anxiety, confusion, delusions, hallucinations, paranoia, psychosis
Renal	Abnormal renal function, acute renal failure
Other	Diaphoresis, fever, hyponatremia, rash

It is possible that these effects are not all related to cathinone use as many users take these substance simultaneously with other drugs and ethanol. Additionally due to lack of reliability and consistency of products, users may not be aware of what drug they have actually taken. Please see text for more information

hyponatremia until further understanding specific to cathinones is reached.

Postmortem

Mephedrone

A decedent with hyponatremia from Sweden is the first reported death related solely to mephedrone [39]. Since that time, other mephedrone-related deaths have been identified. In many of these cases, investigation and analysis are ongoing to determine the role of mephedrone in causing death.

A report on four mephedrone-associated deaths noted that mephedrone was the principle cause of death in one case. A 19-year-old male used mephedrone, MDMA and alcohol, several hours later began to shake and twitch, and then was found “his eyes were rolling and he was choking”. He had cardiorespiratory arrest en route to the hospital and was declared dead on arrival. Postmortem analysis revealed alcohol, 3-trifluoromethylphenylpiperazine, and mephedrone. A second decedent in this series was a 49-year-old woman who developed chest pain and vomiting after insufflating methedrone, drinking alcohol, and smoking cannabis. Her death was attributed to mephedrone, with cardiac fibrosis and atherosclerotic disease as contributing factors. Mephedrone was a contributing factor in two cases: one, a patient with a multidrug overdose and another with a fatal motor vehicle crash [33]. Four additional mephedrone-related deaths are reported: stab wounds were the cause of death in one, mephedrone responsible for two, and the other case unresolved [34]. Accidental death due to multidrug toxicity occurred after use of mephedrone and heroin in a 22-year-old male [32]. Mephedrone was thought to be the cause of death in a person with excited delirium that was aggravated by blood loss from wounds sustained from breaking windows. However, multiple substances were found in the postmortem blood including cocaine, metabolites, and MDMA [40].

Methedrone

Two methedrone-associated deaths classified as accidental have been reported in Sweden. One patient had marked hyperthermia to 42°C. Both patients were found to have pulmonary congestion and edema on postmortem examination [41].

Butylone

Two butylone-associated deaths have been reported. In the first, a man died from injuries due to a fall from height was

also found to have butylone in his blood. In another, a woman reported to have died after ingestion of several drugs, was found to have brain edema, pulmonary congestion and hemorrhages, as well as congestion of the liver, spleen and kidneys. She was noted to have sub-endocardial hemorrhage in the aortic outflow tract as well as contraction band necrosis of the heart [42].

Deaths from use of MDPV and other synthetic cathinones have not been well documented or reported in the medical literature at this time.

Chemistry

Synthetic cathinones are phenylalkylamines derivatives, and are often termed bk-amphetamines due to a ketone attached at the beta position on the amino alkyl chain attached to the phenyl ring [43]. Similar to phenylethylamines like MDMA, they may possess both amphetamine-like properties and the ability to modulate serotonin, causing distinct psychoactive effects. Most cathinone derivatives have sympathomimetic effects; other qualities, including duration and the extent of psychoactive effects, vary based to a large extent on functional group structure. As a group, they are considered to be less potent than their corresponding phenylethylamine analogue due to increased polarity caused by the beta-ketone, resulting in decreased penetration of the blood brain barrier [26].

There are no published human data on the pharmacokinetics and pharmacodynamics of the currently popular synthetic cathinones. A limited understanding of the mechanism of action and metabolism of these drugs is available mostly from in vitro studies and animal models. Amphetamines and derivatives exert their effects by increasing synaptic concentrations of biogenic amines, such as norepinephrine, dopamine, and serotonin. The increases occur via two primary mechanisms. First, these drugs inhibit monoamine uptake transporters, causing decreased clearance of the neurotransmitters from the synapse. Second, they cause release of the neurotransmitters from intracellular stores. Increased intracellular release occurs via changes in vesicular pH as well as inhibition of the vesicular monoamine transport (VMAT2) receptor. VMAT2 is located on the vesicular membrane and responsible for monoamine uptake into the vesicles for storage [44].

In comparison to amphetamines and MDMA, understanding of the mechanism of action of synthetic cathinones is limited. However, based on similarities in structure, similar mechanisms are expected. This assumption is supported by user reports which suggest there are both stimulant effects (use is compared to amphetamine use) and psychoactive effects (compared to use of MDMA or LSD) [28]. Furthermore, in an animal model, synthetic cathinones

were found to be substitutes for rats trained to recognize administration of amphetamine and MDMA [45].

Mechanism: Methylone

Methylone was found to be equally as potent as methamphetamine and MDMA at inhibiting reuptake of norepinephrine and dopamine in human platelets due to inhibition of monoamine uptake transporters [44, 46]. There is some controversy in the literature about its potency at serotonin reuptake inhibition compared to other amphetamine derivatives, with several studies finding decreased potency and at least one study finding no difference [44, 46, 47]. Methylone was significantly less potent at VMAT2 receptor inhibition than methamphetamine and MDMA [44]. Interestingly, inhibition of NE reuptake was competitive, while inhibition at serotonin and dopamine receptors was noncompetitive [44]. Additionally, methylone inhibition may cause reverse transport of neurotransmitters from the nerve terminal into the synapse, as is described with methamphetamine [46].

Mechanism: Mephedrone

Brain concentrations of dopamine in rats given a single dose of 3 mg/kg of mephedrone peaked in 20 min, and returned to baseline in 100–120 min. When compared to MDMA, it was less potent at increasing serotonin brain concentrations, but caused a greater increase in dopamine. The rate of return of neurotransmitters to the baseline concentration was rapid, ten times faster than the rate of return with MDMA and two times faster when compared to amphetamine [48].

Mechanism: Pyrovalerone

Pyrovalerone has inhibitory effects on both norepinephrine and dopamine reuptake [49–51] but in a single study, had little effect on serotonin reuptake. Examination of the chirality of the compound revealed the *S*-enantiomer to be the more biologically active than the *R*-enantiomer [52].

Understanding of the metabolism of synthetic cathinones is also limited with most of the information described derived from animal models.

Metabolism: Pyrovalerone

Pyrovalerone kinetics in mice given both oral and intravenous injections revealed rapid absorption, with only 29% of the dose remaining in the stomach 30 min after ingestion. Four hours after ingestion 70% had been excreted in the urine. After intravenous injection, metabolites were identified in the urine after 5 min and 20% had been excreted in 20 min. Ninety percent was eliminated as metabolites in the

urine and 6–8% as the parent compound in the feces. The highest concentrations of the drug were found in the bile, liver, and kidney with the highest concentrations found 30 min after oral administration. A very small fraction, less than 1%, was found in the brain. In the mice and in one human volunteer, no pyrovalerone was found in the urine, the major metabolite found was 4-(1-pyrrolidinylvaleroyl) benzoic acid [53].

Metabolism: Methylone, Ethylone, Butylone

The metabolism of this group of cathinones is best characterized. Some of the parent compounds are excreted unchanged in the urine. Primary metabolism begins with demethylation of the methylenedioxy ring, followed by catechol *O*-methyltransferase (COMT) mediated *O*-methylation into 4'-hydroxy-3'-methoxy (4'-OH-3'-MeO) or 3'-hydroxy-4'-methoxymethcathinone (3'-OH-4'-MeO). These metabolites are partially conjugated with glucuronides and sulfates and excreted in the urine [54]. *N*-dealkylation is another possible pathway for metabolism, but appears to play a minimal role. Some *bk*-amphetamines can be reduced at the ketone group to the corresponding amino alcohols. This appears to be a minor pathway for butylone and ethylone in humans, which is not utilized for methylone [43].

Analysis of the urine of rats after a 5 mg/kg dose of methylone revealed that 4'-hydroxy-3'-methoxymethcathinone was the most common metabolite, followed by 3'-hydroxy-4'-methoxymethcathinone, methylone, and 3,4-methylenedioxycathinone. Both methylone and 4'-hydroxy-3'-methoxymethcathinone concentrations peaked 4 h after parent drug administration. Methylone was undetectable 36 h after exposure, while 4'-hydroxy-3'-methoxymethcathinone persisted for 48 h after. Analysis of urine of one human user showed similar metabolites to those found in the rat [55].

Metabolism: Mephedrone

N-demethylation to a primary amine, followed by reduction of the ketone moieties to alcohols, then oxidation of the tosyl group to the corresponding alcohol. Some of the alcohols are conjugated via sulfation or glucuronidation and excreted in the urine [56].

Metabolism: MDPV

Metabolism in human liver cells appears similar to that of other synthetic cathinones. Examination of MDPV metabolism in human liver cells revealed the following steps. First, opening of the methylenedioxy ring, followed by demethylation leading to a catechol ring which is subsequently

methylated by COMT. Glucuronidation and sulfation of some metabolites follow. In this one study, 80% of MDPV was unmetabolized, 10% was metabolized to methylcatechol pyrovalerone and 7% to catechol pyrovalerone, though the authors postulated this could have resulted from the very high concentrations of MDPV used [57]. In another study based on examination of rat urine, MDPV underwent a more complicated metabolism, including oxidative and hydroxylation steps. In this same study, MDPV was found to be metabolized *in vitro* by CYP isoenzymes 2C19, 2D6, and 1A2 [58].

Cytotoxic effects of methylone have been found in rat hepatocytes and hamster ovarian cells [46, 59]. Mitochondrial dysfunction due to uncoupling of oxidative phosphorylation was thought to be the source of the cytotoxicity in the hepatocytes [59].

Addiction and Withdrawal

There is currently no focused research on the addiction potential or withdrawal syndromes related to synthetic cathinones. A survey of 1,500 mephedrone users found that over 50% consider it to be addictive [27]. In a telephone survey of 100 mephedrone users, nearly half reported continuous use for more than 48 h. Over 30% reported having more than three of the Diagnostic and Statistical Manual IV criteria for dependence including increased tolerance, continuing to take despite having problems with use and impaired control of use. Fifteen percent reported that friends or family had expressed concern over their mephedrone use [17]. In a Scottish survey of 1,006 students, daily use was reported 4.4% of users, all of whom were less than 21 years of age. The highest frequency of daily use was in the 11–15-year age group. In the same study, 17.5% of users reported “addiction/dependence” symptoms [18]. One case report describes a patient who fulfilled criteria for addiction to mephedrone after 18 months of daily use [60].

Users describe strong cravings to repeat or increase doses after taking mephedrone. Users describe this feeling as the drug being very “moreish”, meaning that it causes the user to want to ingest more shortly after use [11, 28, 61], and call taking multiple doses in succession “fiending” [62].

A physical withdrawal syndrome has not been reported although users report feelings of depression and anxiety at the end of use. In one study, 25% of users reported urges or cravings to continue using [17].

Laboratory Analysis

Synthetic cathinones can be identified using gas chromatography–mass spectrometry or liquid chromatography–mass

spectrometry techniques [63–65]. They can be measured in blood, urine, and stomach contents in both pre and postmortem specimens. Correlation of concentrations with clinical effects is not well understood.

Blood concentrations of methedrone in specimens taken from suspected drug offenders ranged in one series from 0.2 to 4.8 µg/g blood [41].

Mephedrone concentrations in urine specimens taken after use in the preceding 24 h ranged from 0.6 to 7.35 mg/mL [17]. Concentrations in postmortem blood specimens in mephedrone-related deaths have ranged from 0.13 to 22 mg/L [33, 34]. Gastric contents in one case were found to have a concentration of mephedrone of 1.04 mg/L [40].

Postmortem butylone concentrations in the blood have been reported ranging from 0.435 to 1.2 mg/L and in gastric contents at 5.2 mg/L [42].

Synthetic cathinones can be analyzed in hair. A rat model suggests that cathinone and methcathinone are poorly incorporated into hair, but that methylone is well incorporated [66]. Mephedrone has been found in human hair on postmortem examination in concentrations of 4.2–4.7 ng/mL [34]. Methedrone has also been found in postmortem concentration of 29–37 ng/mL [41].

Legal Status

The legal status of the synthetic cathinones is variable among countries and is changing rapidly. Until recently in the United States, they were unscheduled, but illegal for human consumption under the Federal Analogue Act of 1986. This law was passed in an attempt to prevent use of “designer drugs” which were analogs of other illegal drugs of abuse manufactured with small chemical changes to subvert existing regulatory laws. This law does not criminalize possession or manufacture of the substances, unless intended for human consumption [67]. However, on September 7 2011, the DEA used its emergency scheduling authority to enact temporary control scheduled to begin in approximately 30 days. Possession or sale of mephedrone, MDPV and methylone will be illegal for 1 year while further evaluation is undertaken to consider the need for permanent control [68]. In December of 2010, mephedrone was banned throughout the European Union [69].

Conclusion

The dramatic rise of the synthetic cathinones as novel drugs of abuse highlights ways in which the Internet is modulating use of drugs by increasing information sharing through drug use websites and increasing availability of drugs by expanding access for purchase. Exposure to and use of

synthetic cathinones are increasingly popular despite a lack of scientific research and understanding of the potential harms of these substances. The clinical similarities to amphetamines and MDMA specifically are predictable based on the chemical structure of this class of agents. More work is necessary to understand the mechanisms of action, toxicokinetics, toxicodynamics, metabolism, clinical and psychological effects as well as the potential for addiction and withdrawal.

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References

- James D, Adams RD, Spears R et al (2010) Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. *Emerg Med J*. Epub ahead of print
- Google, Insights for search (2011) <http://www.google.com/insights/search/>. Last accessed 7/1/2011
- Al-Motareb A, Al-Habori M, Broadley KJ (2010) Khat chewing, cardiovascular disease and other internal medical problems; the current situation and directions for future research. *J Ethnopharmacol* 132:540–548
- Hyde JF, Browning E, Adams R (1928) Synthetic homologs of D, L-ephedrine. *J Am Chem Soc* 50(8):2287–2292
- Saen de Burnaga Sanchez J (1929) Sur un homologue de la Société Chimique de France. 45:284–6
- Advisory Council on the Misuse of Drugs. Consideration of the cathinones. <http://www.homeoffice.gov.uk/publications/alcohol-drugs/drugs/acmd1/acmd-cathinones-report-2010?view=Binary>. Last accessed 7/1/2010
- Emerson TS, Cisek JE (1993) Methcathinone: a Russian designer amphetamine infiltrates the rural Midwest. *Ann Emerg Med* 22(12):1897–1903
- Gardos G, Cole JO (1971) Evaluation of pyrovalerone in chronically fatigued volunteers. *Curr Ther Res Clin Exp* 13(10):631–635
- Goldberg J, Gardos G, Cole JO (1973) A controlled evaluation of pyrovalerone in chronically fatigued volunteers. *Int Pharmacopsychiatry* 8(1):60–69
- Krükku P, Wilhelm L, Schwarz O, Rintatalo J (2011) New designer drug of abuse: 3,4-methylenedioxypyrovalerone (MDPV). Findings from apprehended drivers in Finland. *Forensic Sci Int* 210(1–3):195–200
- Psychonaut WebMapping Research Group (2009) Mephedrone. Report. London, UK, Institute of Psychiatry, King's College London
- Archer RP (2009) Fluoromethcathinone, a new substance of abuse. *Forensic Sci Int* 185(1–3):10–20
- Centers for Disease Control and Prevention (2011) Emergency department visits after use of a drug sold as “bath salts”–Michigan, November 13, 2010–March 31, 2011. *MMWR Morb Mortal Wkly Rep* 60(19):624–627
- The Poison Review. <http://www.thepoisonreview.com/2010/11/30/2093/>. Last accessed 6/10/2001
- Measham F, Moore K, Newcombe R, Welch Z (2010) Tweaking, bombing, dabbing and stockpiling: the emergence of mephedrone and the perversity of prohibition. *Drug Alcohol Today* 10(1):14–21
- Brunt TM, Poortman A, Niesink RJ, van den Brink W (2010) Instability of the ecstasy market and a new kid on the block: mephedrone. *J Psychopharmacol*. Epub ahead of print
- Winstock AR, Mitcheson LR, Deluca P et al (2011) Mephedrone, new kid for the chop? *Addiction* 106(1):154–161
- Dargan PI, Albert S, Wood DM (2010) Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. *QJM* 103(11):875–879
- McNamara S, Stokes S, Coleman N (2010) Head shop compound abuse amongst attendees of the Drug Treatment Centre Board. *Int Med J* 103(5):134–137
- American Association of Poison Control Centers. www.aapcc.org/dnn/default.aspx. Last accessed 7/10/2010
- Ramsey J, Dargan PI, Smyllie M et al (2010) Buying ‘legal’ recreational drugs does not mean that you are not breaking the law. *QJM* 103(10):777–783
- Brandt SD, Summall HR, Measham F, Cole J (2010) Second generation mephedrone. The confusing case of NRG-1. *BMJ* 341:c3564
- The Misuse of Drugs (Amendment) (England, Wales and Scotland) Regulations 2010. <http://www.legislation.gov.uk/uksi/2010/1144/made>. Last accessed 7/22/2010
- Davies S, Wood DM, Smith G et al (2010) Purchasing ‘legal highs’ on the Internet—is there consistency in what you get? *QJM* 103(7):489–493
- Winstock AR, Mitcheson LR, Marsden J (2010) Mephedrone: still available and twice the price. *Lancet* 376(9752):1537
- EMCDDA–Europol joint report on mephedrone. <http://www.emcdda.europa.eu/online/annual-report/2010/boxes/p92>. Last accessed 7/12/2010
- Carhart-Harris RL, King LA, Nutt DJ (2011) A web-based survey on mephedrone. *Drug Alcohol Depend*. Epub ahead of print
- Newcombe R (2009) Mephedrone: use of mephedrone (M-Cat, Meow) in Middlesbrough, Liffelinc, Manchester, UK
- Wood DM, Davies S, Puchnarewicz M et al (2010) Recreational use of mephedrone (4-methylmethcathinone, 4-MMC) with associated sympathomimetic toxicity. *J Med Toxicol* 6(3):327–330
- Dargan P, Wood D (2010) Technical report on mephedrone, 2010. European Monitoring Centre for Drugs and Drug Addiction. Risk assessment report of a new psychoactive substance: 4-methylmethcathinone (mephedrone). EMCDDA, Lisbon
- Wood DM, Greene SL, Dargan PI (2011) Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. *Emerg Med J* 28(4):280–282
- Dickson AJ, Vorce SP, Levine B, Past MR (2010) Multiple-drug toxicity caused by the coadministration of 4-methylmethcathinone (mephedrone) and heroin. *J Anal Toxicol* 34(3):162–168
- Maskell PD, De Paoli G, Seneviratne C, Pounder DJ (2011) Mephedrone (4-methylmethcathinone)-related deaths. *J Anal Toxicol* 35(3):188–191
- Torrance H, Cooper G (2010) The detection of mephedrone (4-methylmethcathinone) in 4 fatalities in Scotland. *Forensic Sci Int* 202(1–3):e62–e63
- Regan L, Mitchelson M, Macdonald C (2010) Mephedrone toxicity in a Scottish emergency department. *Emerg Med J*. Epub ahead of print
- Henry JA, Fallon JK, Kicman AT, Hutt AJ, Cowan DA, Forsling M (1998) Low-dose MDMA (“ecstasy”) induces vasopressin secretion. *Lancet* 351(9118):1784
- Sammiler EM, Foley PL, Lauder GD et al (2010) A harmless high? *Lancet* 376(9742):742
- Wood DM, Davies S, Greene SL et al (2010) Case series of individuals with analytically confirmed acute mephedrone toxicity. *Clin Toxicol (Phila)* 48(9):924–927
- Gustavsson D, Escher C (2009) Mephedrone—Internet drug which seems to have come and stay. Fatal cases in Sweden have

- drawn attention to previously unknown substance. *Lakartidningen* 106(43):2769–2771
40. Lushhof KJ, Oosting R, Maes A et al (2011) A case of extreme agitation after use of mephedrone in the Netherlands. *Forensic Sci Int* 206(1–3):e9395
 41. Wikström M, Thelander G, Nyström I, Kronstrand R (2010) Two fatal intoxications with the new designer drug methedrone (4-methoxymethcathinone). *J Anal Toxicol* 34(9):594–598
 42. Carter N, Ruddy GN, Milroy CM, Forrest AR (2000) Deaths associated with MBDB misuse. *Int J Legal Med* 113(3):168–170
 43. Zaitzu K, Katagi M, Tatsuno M et al (2011) Recently abused b-keto derivatives of 3,4-methylenedioxyphenylalkylamines: a review of their metabolisms and toxicological analysis. *Forensic Toxicol* 29(2):73–84
 44. Cozzi NV, Sievert MK, Shulgin AT et al (1999) Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. *Eur J Pharmacol* 381(1):63–69
 45. Dal Cason TA, Young R, Glennon RA (1997) Cathinone: an investigation of several N-alkyl and methylenedioxy-substituted analogs. *Pharmacol Biochem Behav* 58(4):1109–1116
 46. Sogawa C, Sogawa N, Ohyama K et al (2011) Methylone and monoamine transporters: correlation with toxicity. *Curr Neuropharmacol* 9:58–62
 47. Nagai F, Nonaka R, Satoh Hisashi, Kamimura K (2007) The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. *Eur J Pharmacol* 559(2–3):132–137
 48. Kehr J, Ichinose F, Yoshitake S et al (2011) Mephedrone, compared to MDMA (ecstasy) and amphetamine, rapidly increases both dopamine and serotonin levels in nucleus accumbens of awake rats. *Br J Pharmacol*. Epub ahead of print
 49. Bonnet JJ, Protais P, Chagraoui A, Costentin J (1986) High-affinity [3H]GBR 12783 binding to a specific site associated with the neuronal dopamine uptake complex in the central nervous system. *Eur J Pharmacol* 126(3):211–222
 50. Servin A, Fauquet JP, Jacquot C, Rapin JR (1978) Effects of pyrovalerone on peripheral noradrenergic mechanisms. *Biochem Pharmacol* 27(12):1693–1694
 51. Vaugeois JM, Bonnet JJ, Costentin J (1992) In vivo labelling of the neuronal dopamine uptake complex in the mouse striatum by [3H]GBR 12783. *Eur J Pharmacol* 210(1):77–84
 52. Meltzer PC, Butler D, Deschamps JR, Madras BK (2006) 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem* 49(4):1420–1432
 53. Michaelis W, Russel JH, Schindler O (1970) The metabolism of pyrovalerone hydrochloride. *J Med Chem* 13(3):497–503
 54. Zaitzu K, Katagi M, Kamata HT et al (2009) Determination of the metabolites of the new designer drugs bk-MBDB and bk-MDEA in human urine. *Forensic Sci Int* 188(1–3):131–139
 55. Kamata HT, Shima N, Zaitzu K et al (2006) Metabolism of the recently encountered designer drug, methylone, in humans and rats. *Xenobiotica* 36(8):709–723
 56. Meyer MR, Wilhelm J, Peters FT, Maurer HH (2010) Beta-keto amphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone, and methylone in urine using gas chromatography-mass spectrometry. *Anal Bioanal Chem* 397(3):1225–1233
 57. Strano-Rossi S, Cadwallader AB, de la Torre X, Botrè F (2010) Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom* 24(18):2706–2714
 58. Meyer MR, Du P, Schuster F, Maurer HH (2010) Studies on the metabolism of the α -pyrrolidinophenone designer drug methylenedioxy-propylvalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom* 45(12):1426–1442
 59. Nakagawa Y, Suzuki T, Tayama S, Ishii H, Ogata A (2009) Cytotoxic effects of 3,4-methylenedioxy-N-alkylamphetamines, MDMA and its analogues, on isolated rat hepatocytes. *Arch Toxicol* 83(1):69–80
 60. Bajaj N, Mullen D, Wylie S (2010) Dependence and psychosis with 4-methylmethcathinone (mephedrone) use. *BMJ Case Reports*. Epub ahead of print
 61. Erowid. http://www.erowid.org/chemicals/4_methylmethcathinone/4_methylmethcathinone_effects.shtml Last accessed 7/12/2010
 62. Schifano F, Albanese A, Fergus S et al (2011) Mephedrone (4-methylmethcathinone; ‘meow meow’): chemical, pharmacological and clinical issues. *Psychopharmacology* 214(3):593–602
 63. Frison G, Gregio M, Zamengo L et al (2011) Gas chromatography/mass spectrometry determination of mephedrone in drug seizures after derivatization with 2,2,2-trichloroethyl chloroformate. *Rapid Commun Mass Spectrom* 25(2):387–390
 64. Maheux CR, Copeland CR (2010) Characterization of three methcathinone analogs: 4-methylmethcathinone, methylone, and bk-MBDB. *DEA Microgram J* 7(2):42–49
 65. Wissenbach DK, Meyer MR, Remane D, Philipp AA, Weber AA, Maurer HH (2011) Drugs of abuse screening in urine as part of a metabolite-based LC-MS(n) screening concept. *Anal Bioanal Chem* 400(10):3481–3489
 66. Kikura-Hanajiri R, Kawamura M, Saisho K, Kodama Y, Goda Y (2007) The disposition into hair of new designer drugs; methylone, MBDB and methcathinone. *J Chromatogr B Analyt Technol Biomed Life Sci* 855(2):121–126
 67. Federal Analogue Act. Controlled Substance Analogue Enforcement Act of 1986, Pub. L. No. 99–570, § 1203, 100 Stat. 3207, 3213–14
 68. DEA moves to emergency control synthetic stimulants. <http://www.justice.gov/dea/pubs/pressrel/pr090711.html>. Last accessed 09/07/2011
 69. Europa. Commission achieves EU-wide ban on ecstasy-like drug mephedrone <http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/10/646>. Last accessed 6/14/2010
 70. Frolich S, Lambe E, O’Dea J (2011) Acute liver failure following recreational use of psychotropic “head shop” compounds. *Ir J Med Sci* 180(1):263–264
 71. Nicholson PJ, Quinn MJ, Dodd JD (2010) Headshop heartache: acute mephedrone ‘meow’ myocarditis. *Heart* 96(24):2051–2052
 72. Shimizu E, Watanabe H, Kojima T et al (2007) Combined intoxication with methylone and 5-MeO-MIPT. *Prog Neuro-psychopharmacol Biol Psychiatry* 31(1):288–291

65

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Development of a rapid LC-MS/MS method for direct urinalysis of designer drugs

Charlotte Bell,^a Claire George,^{b*} Andrew T. Kicman^a and Allan Traynor^b

The current immunoassay screening methodologies used to detect sympathomimetic amines within the context of workplace drug testing may fail to detect a number of the emerging designer drugs, for example β -keto amphetamines and piperazine derivatives, commonly referred to as 'legal highs'. Therefore, a rapid multi-analyte qualitative screening method, using ultra-high-pressure liquid chromatography-tandem mass spectrometry (LC-MS/MS), was investigated for analysis of new designer drugs that have emerged from the former legal highs market.

Eight analytes were targeted as model compounds: 4-methylmethcathinone (mephedrone), 3,4-methylenedioxymethcathinone (bk-MDMA, 'methyone'), 2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one (bk-MBDB, 'butylone'), 4-methoxymethcathinone (bk-PMMA, 'methedrone'), 1-benzylpiperazine (BZP), 1-(3-trifluoromethyl phenyl)-piperazine (TFMPP), 1-(3-chloro phenyl)-piperazine (mCPP), and 3, 4-methylenedioxypropylvalerone (MDPV).

The LC-MS/MS method developed encompassed direct analysis following a 1:4 dilution of urine with mobile phase to reduce matrix effects. Although not all compounds were completely resolved chromatographically, two product ions conferred sufficient specificity to allow target analyte identification. Although all target analytes were readily detected at 500 ng/ml, a cut-off of 1000 ng/ml was chosen to mirror the amphetamine screening cut-off commonly used for routine analysis of workplace drug testing samples.

In conclusion, direct analysis using LC-MS/MS offers an attractive way forward for the development of a rapid routine screen for new psychoactive substances, particularly given the growing number of novel compounds. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: direct analysis; LC-MS/MS; designer drugs

Introduction

The term 'designer drug' encompasses both synthetically altered, naturally occurring compounds and substances which have been entirely designed from molecular level upwards, all of which have psychoactive properties.^[1,2]

Archetypal designer drugs include amphetamines, methamphetamine and 3, 4-methylenedioxymethamphetamine (MDMA). Legislation against such drugs has resulted in the synthesis of alternative analogues marketed as 'legal' or 'herbal highs' – substances not subject to control under the Misuse of Drugs Act (1971).^[3] This is achieved by manipulation of functional groups on the structural backbone as an attempt to evade legislation.

These new designer drugs are predominantly phenylethylamine, piperazine, tryptamine, pyrrolidinophenone, and phenylcyclohexyl derivatives.^[2] Such is their rapid emergence that minimal scientific information is available regarding their pharmacotoxicology, making detection and determination more complex. Reportedly all confer a similar mechanism of action to amphetamine and/or MDMA, i.e. sympathomimetic stimulation and/or empathogenic effects respectively dependent on their exact configuration.^[4,5]

Control measures have come into effect in the UK targeting these new psychoactive substances and similar legislation is being considered in several other countries. Detection and determination of these new designer drugs (Figure 1a–1h) as part of a workplace drug testing program is increasingly expected because they are being administered as 'recreational replacements' for their more well-known counterparts (Figure 1i–k).

Immunoassay is commonly used for preliminary screening of abused drugs in urine and is an integral part of the approach used for testing samples collected as part of a workplace drug testing program.^[6] Hybridoma production (including the period of immunization) seldom takes less than two months from start to finish, and it can take well over a year^[7] combined with the further development to launch a consistent commercial immunoassay for drug screening purposes; the whole process is time consuming. Given the diversity of these new designer drugs combined with their ever changing popularity and availability, that the development of new immunoassays to specifically target these drugs is unlikely to be financially viable.^[2] Currently there are no immunoassay available which specifically target new psychoactive substances, for example, β -keto amphetamines and piperazine derivatives.

The lack of a suitable immunoassay means that a rapid alternative technique is necessary to enable detection of such compounds.^[10] Although common, gas chromatography mass spectrometry (GC-MS) is not an ideal alternative to immunoassay screening because of the protracted preparative requirements, including extraction often followed by derivatization of the

* Correspondence to: Claire George, Concateno, Harbour Quay, 100 Preston's Road, London E14 9PH, UK. E-mail: Claire.George@concateno.com

^a Department of Forensic Science and Drug Monitoring, Kings College London, School of Biomedical and Health Sciences, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH

^b Concateno, Harbour Quay, 100 Preston's Road, London E14 9PH

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Direct LC-MS/MS for designer drugs

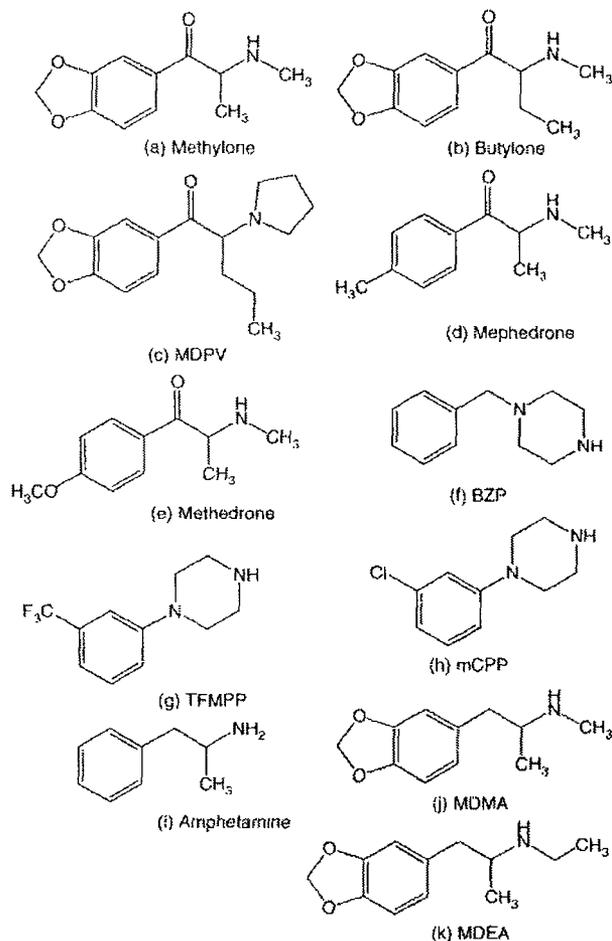


Figure 1. Examples of new (a–h) designer drugs recently legislated against and some of their traditional designer drug counterparts (i–k). Drugs a–e are beta-keto amphetamines (cathinone derivatives), and examples f–h are piperazine derivatives.

amine function of these fairly polar drugs.^[8] LC-MS/MS has the potential to screen for multiple analytes within one assay but it is susceptible to matrix effects.^[9,10,16] This phenomenon must be considered for each analyte of interest and several approaches exist to evaluate the extent of matrix effects on a particular assay.^[11,13] Validated screening methodologies using LC-MS have been developed, although these have predominantly used liquid-liquid extraction (LLE) or solid-phase extraction (SPE) thus increasing sample analysis time.^[1,2] A direct analysis approach has been used in several bioanalytical areas for many years, such as metabolic fingerprinting, and is now being increasingly applied for the determination of drugs in urine, for example having been demonstrated to be robust and reliable for the confirmatory analysis of the amphetamines.^[13] Moreover, direct injection has been routinely used for the screening of some of the more common drugs of abuse within the Concateno laboratories for the last eight years. There is, however, minimal information regarding the use of 'dilute and shoot' for direct analysis of designer drugs such as those in this report.

The aim of this study was to develop a rapid, multi-analyte qualitative screening method using ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) to specifically identify the most recently legislated against designer drugs in urine (Figure 1a–h). The use of direct analysis, rapid

chromatography and short analysis times could make it attractive as a viable addition to the immunochemical screening panel used for workplace drug testing.

In addition, the cross reactivity of some of the new designer drugs (Figure 1a–h) in the CEDIA[®] amphetamine/ecstasy assay was investigated.

Experimental

Chemicals and reagents

The following drug standards were obtained from Sigma Aldrich (Poole, Dorset, UK); 4-methylmethcathinone (mephedrone), 3,4-methylenedioxy-methcathinone (bk-MDMA, 'methylone'), 2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one (bk-MBDB, 'butylone'), 4-methoxymethcathinone (bk-PMMA, 'methedrone'), 1-benzylpiperazine (BZP), 1-(3-trifluoromethyl phenyl)-piperazine (TFMPP) and 1-(3-chloro phenyl)-piperazine (mCPP). A sample of 3,4-methylenedioxy-pyrovalerone (MDPV) was kindly provided by John Ramsey, TICTAC Communications, St Georges University of London. The deuterated internal standards; amphetamine-d₅, 3,4-methylenedioxy-methamphetamine-d₅ (MDMA-d₅), methylenedioxyamphetamine-d₅ (MDA-d₅) and methylenedioxyethylamphetamine-d₅ (MDEA-d₅) were purchased from LGC Standards (Teddington, UK). HPLC grade methanol, ammonium acetate, acetonitrile, and analytical grade formic acid were purchased from Fisher Scientific (Loughborough, UK).

Stock standard solutions (1 mg/ml) of each analyte were prepared in methanol and used to prepare methanolic working solutions of the individual analytes at concentrations of 100 µg/ml and 10 µg/ml respectively. A working internal standard solution containing amphetamine-d₅, MDMA-d₅, MDA-d₅ and MDEA-d₅ was prepared at a concentration of 10 µg/ml.

Preparation of calibrators and quality control (QC)

To assess the detection capabilities of the LC-MS/MS screening procedure, calibrators containing mephedrone, methylone, butylone, methedrone, BZP, TFMPP, mCPP and MDPV were prepared daily in drug-free urine prior to analysis at concentrations of 500 ng/ml, 1000 ng/ml and 2000 ng/ml. A limited 3-point calibration curve was considered appropriate because the method would be applied to the qualitative analysis of samples as a preliminary screening procedure.

Combined quality control (QC) samples containing the analytes of interest were prepared independently from the calibrators in drug-free urine, i.e. using a different blank matrix to that used for the preparation of calibrators, at a concentration of 1000 ng/ml. These were stored in 5-ml aliquots at -20 °C prior to analysis.

The calibrators, together with the QC samples, were analyzed alongside each run and used to assess the method performance (reproducibility, %CV) as well as the stability of samples under storage conditions.

A 'carry over' standard was prepared at a concentration of 50 000 ng/ml by spiking all of the analytes of interest into drug-free urine. The carry over standard was run at the beginning and the end of each analytical run and was immediately followed by a 'blank' sample to ensure that any analyte carry over would be detected.

Table 1. List of analytes including relevant deuterated (d₅) internal standards, together with their respective mass spectrometry parameters

Drug name	Retention time (t _R /min)	Q1 mass (amu)	Q3 mass (amu)	Cone (V)	Collision energy (kV)
BZP	1.27	176.1	90.7	25.0	27.0
	1.27		84.7	25.0	25.0
Methylone	1.79	208.0	159.9	20.0	20.0
	1.79		131.9	20.0	27.0
Amphetamine-d ₅	1.86	141.0	124.0	12.0	12.0
MDA-d ₅	1.96	185.0	168.0	17.0	15.0
Methedrone	2.02	193.9	175.9	22.0	15.0
	2.02		160.9	22.0	25.0
MDMA-d ₅	2.09	199.0	165.0	20.0	15.0
Butylone	2.17	222.0	203.9	20.0	20.0
	2.17		173.9	20.0	22.0
MDEA-d ₅	2.28	213.0	163.0	25.0	12.0
Mephedrone	2.28	177.9	159.9	22.0	20.0
	2.28		144.8	22.0	25.0
mCPP	2.75	196.0	153.8	37.0	25.0
	2.75		118.8	37.0	32.0
MDPV	2.89	276.1	174.9	35.0	35.0
	2.90		148.9	35.0	35.0
TFMPP	3.24	231.0	188.0	35.0	32.0
	3.24		44.0	35.0	35.0

Immunoassay screening

To establish the immunoreactivity of the target analytes with the CEDIA[®] Amphetamines/Ecstasy immunoassay, individual drug standards at concentrations of 1000 ng/ml, 5000 ng/ml, and 10 000 ng/ml were prepared in drug-free blank urine.

The standards were analyzed according to the manufacturer's instructions using an Olympus AU2700 (High Wycombe, Beckman Coulter, UK) in conjunction with the CEDIA[®] Amphetamines/Ecstasy assay (Microgenics, Fremont, CA, USA) using a 1000 ng/ml d-methamphetamine standard as the cut-off calibrator.

QC samples were prepared from commercially available material at ±20% of the assay cut-off and run alongside the standards to ensure acceptable assay performance.

LC-MS sample preparation

A 1-ml aliquot of sample check/sample/QC/calibrator was prepared for analysis by centrifuging at 15 830 g for 5 min. Following the addition of 50 µl of internal standard solution (10 µg/ml) samples were vortex mixed for 10 s and then diluted 1:4 (v/v) with 98% 20 mM ammonium acetate, adjusted to pH using 0.1% formic acid 3:2% acetonitrile. The samples were then directly injected into the LC-MS system.

Instrumentation

Chromatography

Analysis was performed using a Waters Acquity ultra performance liquid chromatography (UPLC) system (Waters, Elstree, UK). Chromatographic separation was achieved using an Acquity UPLC BEH C18 2.1 × 50 mm column with 1.7 µm particle size fitted with a 0.2 µm stainless steel Acquity column in line filter unit (Waters, Elstree, UK). The mobile phase consisted of solvent A (20 mM ammonium formate/0.1% formic acid, pH 3) and solvent

B (acetonitrile/0.1% formic acid). A gradient method was used starting with 2% B, ramping to 25% B by 2.5 min. Following a 1-min hold period, it was then subsequently increased to 40% B by 4.2 min and then rapidly returned to starting conditions by 4.3 min. The total run time was 5 min. The flow rate was set at 0.400 ml/min with an injection volume of 15 µl. The auto-sampler was kept at 20 °C and column temperature set to 35 °C.

Mass spectrometry

Analyses were performed using a Quattro Premier XE triple quadrupole mass spectrometer (Waters, Elstree, UK) using electrospray ionisation in the positive mode. The following parameters were optimised and used during analysis; capillary voltage 1.00 kV; source temperature 120 °C; desolvation temperature 400 °C; desolvation gas flow rate 887 l/hr. Direct infusion of the individual analytes under investigation was used to identify the molecular ion (M + H⁺) followed by a product ion scan to identify the most prominent fragments following collision energy optimisation. This information was used to determine the appropriate selected reaction monitoring (SRM) transitions which were used during analysis (Table 1). Due to the lack of availability of deuterated internal standards for the compounds studied, deuterated amphetamine, MDA, MDMA and MDEA were added as chromatographic markers for the following:- Amphetamine-d₅: BZP and Methylone; MDA-d₅: Methedrone; MDMA-d₅: Butylone; MDEA-d₅: Mephedrone, mCPP, MDPV and TFMPP. To ensure continued sensitivity of the method, the cone was cleaned daily prior to use.

Data acquisition, data review and instrument controls were performed using MassLynx and Targetlynx software (Waters, Elstree, UK).

Limit of detection, limit of quantitation, matrix effects, and analyte recovery

There are several approaches which can be used to calculate the limit of detection (LOD) and limit of quantitation (LOQ) of an

Direct LC-MS/MS for designer drugs

Table 2. Results generated in the CEDIA amphetamine/ecstasy assay following the analysis of drug-free urine spiked with β -keto amphetamines and piperazine derivatives

Sample type	Apparent concentration (ng/ml), 10 000 ng/ml solution	Apparent concentration (ng/ml) 5000 ng/ml solution	Apparent concentration (ng/ml) 1000 ng/ml solution
Butylone	1592	646	239
Methylone	369	176	37
Methedrone	244	141	53
Mephedrone	211	88	67
BZP	435	254	60
TFMPP	850	459	101
mCPP	847	463	64
MDPV	169	94	10

analytical method. Since the method described is qualitative and incorporates the use of a relatively high analytical cut-off (1000 ng/ml) to reflect the cut-off commonly applied when screening using an amphetamine immunoassay, the LOD and LOQ were estimated from the signal to noise (S/N) of the lowest calibrator (500 ng/ml). A S/N ratio of 3 is recognized as acceptable for estimating LOD with an S/N of 10 being acceptable for the determination of the LOQ. These criteria were applied to the data generated as part of this study.

Matrix effects and recovery were assessed using the direct comparison method as described by Matuszewski *et al.*^[12] Sets of samples containing 500 ng/ml of each working standard and internal standards were prepared in matrix free solvent (0.1% formic acid) and drug-free urine samples from 5 different sources (pH 6–9).

Ion suppression and enhancement was assessed by comparing the peak area of standards in 0.1% formic acid (A) and standards spiked into the urine samples post-dilution (B) and pre-dilution (C):

$$\text{Matrix effect (\%)} = \frac{\text{area ratio of B}}{\text{area ratio of A}} \times 100$$

$$\text{Recovery (\%)} = \frac{\text{area ratio of C}}{\text{area ratio of B}} \times 100$$

Case sample analysis

During the course of the study two samples were submitted to the laboratory specifically for mephedrone analysis. Sample 1 was collected from a known mephedrone user. The second sample was collected from a known associate of the donor of sample 1. The method described was applied to the analysis of these samples.

Results and discussion

Immunoassay screening

Currently neither β -keto amphetamines or piperazine derivatives whether in their parent drug form or their metabolites (where elucidated) are listed as cross-reactants in amphetamine and/or methamphetamine immunoassays.^[2,14] The data presented in this report support this assumption with the results for all target analytes falling well below the 1000 ng/ml cut-off of the immunoassay, with the exception of butylone, where a 10 000 ng/ml concentration produced a positive screening result (Table 2), with an apparent amphetamines concentration of 1592 ng/ml, 16% of the true concentration.

It is not clear why butylone has a higher immunoreactivity than the other analytes studied. According to Loo *et al.*,^[15] when

compared to their non-keto equivalents using the Microgenics multiplex CEDIA Amphetamine/Ecstasy assay, MDMA (the non-keto equivalent of methylone) had the highest cross reactivity (199% when a 250 ng/ml concentration was tested) and not MBDB, (the non-keto equivalent of butylone) which had a 123% cross reactivity when 500 ng/ml was tested.

The piperazine derivatives (Table 2) exhibited a weak cross-reactivity with the CEDIA Amphetamine/Ecstasy assay as demonstrated by the analysis of samples spiked at 5 times and 10 times the assay cut-off. Most immunochemical research appears to have been performed on piperazine derivatives particularly BZP and TFMPP.^[16,17] Using the CEDIA DAU Amphetamine/Ecstasy assay Button and Kenyon^[18] found that BZP and TFMPP did not test positive above the 1000 ng/ml cut-off until concentrations of 150 000 ng/ml and 25 000 ng/ml, respectively were used. This supports earlier research by de Boer *et al.*^[19] using the AxSYM Amphetamine/Methamphetamine II FPIA assay which did not detect urine spiked with 100 000 ng/ml BZP using a 300 ng/ml cut-off. However, some degree of cross-reactivity was observed with the Dade Behring EMIT d.a.u. Amphetamine assay using a cut-off of 300 ng/ml.

Although all the target analytes discussed in this study are thought to act to varying degrees on the same receptors as (S)-amphetamine, the results support previous research which suggests that binding to the same receptors does not ensure that they will also interact with the same assay antibodies as amphetamine.^[8,19]

Chromatographic analysis

Thorough sample preparation is integral before using hyphenated techniques as part of bioanalysis, particularly with the advent of more potent drugs which may be present at lower levels than previously encountered.^[20,21] Yet it is sample preparation, especially if performed manually, that is believed to be a fundamental rate-limiting step to high throughput analysis.

In this study, centrifugation was used in an attempt to remove any particulates as quickly as possible prior to the addition of the internal standard and sample dilution. A dilution factor of 1:4 (v/v) was chosen based on previous in-house (unpublished) research into β -keto amphetamine analysis. The dilution factor chosen is integral because of potential column damage and loss of MS sensitivity.^[22]

The combination of reduced sample preparation time by the use of a simple sample dilution approach together with the use of UPLC chromatographic conditions allowed the development of a fast and accurate analytical method with increased chromatographic



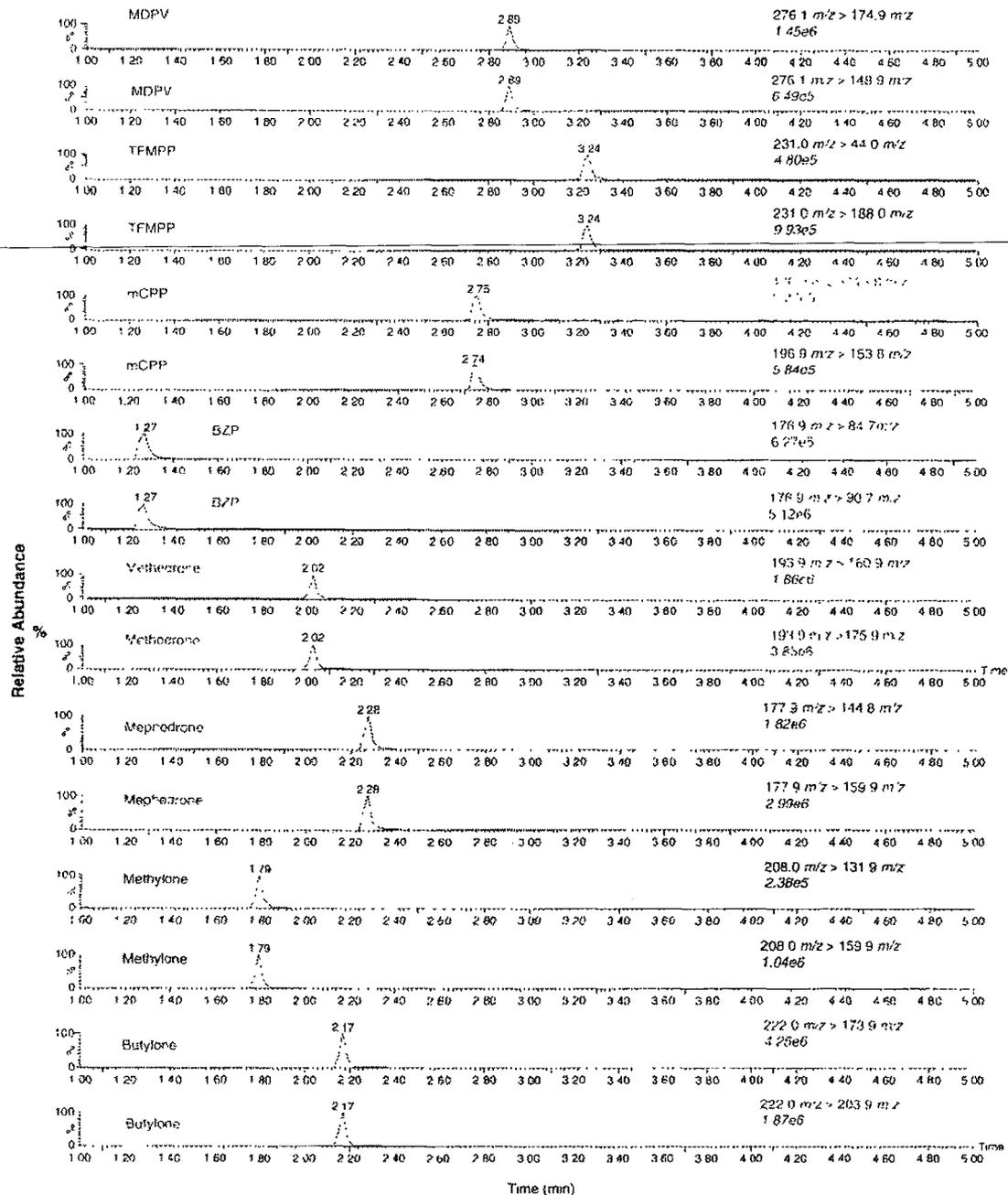


Figure 2. SRM mass chromatograms obtained following the analysis of 500 ng/ml standards prepared in 0.1% formic acid.

resolution and sensitivity.^[10] Not all compounds were completely resolved from each other (Figures 2 and 3) in the chromatographic run adopted (5 min), but two product ions conferred sufficient specificity to allow identification of all eight of the drugs targeted. With the growing number of new psychoactive substances, positional isomers may give rise to identical transitions and without adequate chromatography, these may not be distinguished. Even so, with the 'dilute and shoot' approach, this is not an issue, the emphasis being on the rapid screening of drugs, presumptive positive samples then being subjected to analytical procedures incorporating adequate chromatographic resolution and relative ion intensities for identification purposes. The inter-assay QC data obtained using this method demonstrated acceptable between

run reproducibility, with a CV of 12%. No analyte carry over was detected throughout the study.

It should be noted that retention times for each analyte were reproducible (+/- 2%) despite the lack of a deuterated internal standard. Ideally the method should include a deuterated internal standard for each compound targeted, particularly for the early eluting analytes, as a simple correction technique. For screening procedures, however, using a different internal standard for every analyte is impractical because it starts to reduce SRM sensitivity by introducing too many transitions.

SRM was chosen because of its recognized specificity. Such an approach was ideal for this study because the method was to be developed as a targeted screening approach, i.e. tested against

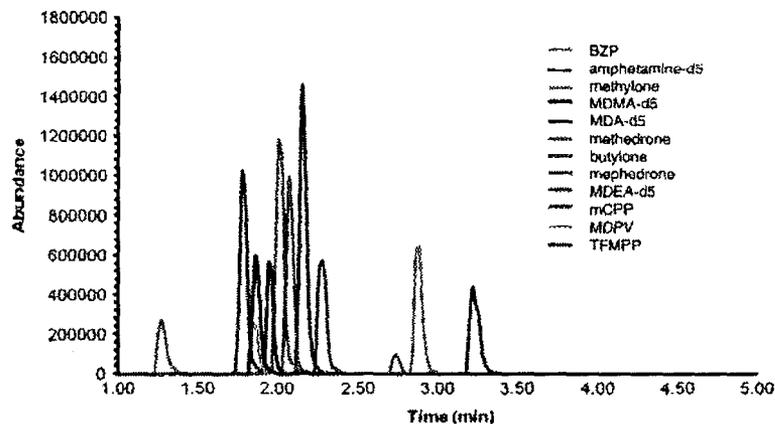


Figure 3. Smoothed chromatogram of the primary transitions (see Table 1) obtained following the analysis of a 500 ng/ml standard prepared in drug-free urine.

Table 3. Limits of detection and limit of quantitation calculated as three times the S/N (LOD) and ten times the S/N (LOQ) following the analysis of the 500 ng/ml standard prepared in drug-free blank urine

Analyte	Estimated Limit of detection (ng/ml) (S/N 3:1)	Estimated Limit of quantitation (ng/ml) (S/N 10:1)
Butylone	2.0	6.5
Methylone	2.8	9.3
Methedrone	2.4	8.0
Mephedrone	2.0	6.8
BZP	8.3	27.3
TFMPP	6.5	21.5
mCPP	29.0	96.0
MDPV	3.4	11.3

Table 4. Matrix effects (mean % \pm SD) and analyte recovery (mean % \pm SD) calculated following the analysis of a 500 ng/ml standard prepared in drug-free blank urine (n = 5)

Analyte	Matrix effects (Mean % \pm SD)	Recovery (Mean % \pm SD)
Butylone	100.1 (\pm 3.09)	93.0 (\pm 7.10)
Methylone	99.9 (\pm 10.7)	97.8 (\pm 9.33)
Methedrone	92.8 (\pm 4.1)	105.3 (\pm 2.40)
Mephedrone	106.8 (\pm 3.7)	96.4 (\pm 3.33)
BZP	75.4 (\pm 1.4)	85.8 (\pm 5.61)
TFMPP	104.9 (\pm 7.7)	79.5 (\pm 5.12)
mCPP	92.6 (\pm 7.7)	88.2 (\pm 3.10)
MDPV	108.0 (\pm 0.9)	77.2 (\pm 3.25)

a panel of selected compounds. This approach is not suitable for analysis of complete unknowns.^[23]

Numerous reports^[24–26] state that three ions or at least two SRM transitions should be chosen, preferably including the molecular ion, as was performed in this study to increase selectivity of the technique. This highlights that not only are the specific transitions important for selective and sensitive detection but also the analyte specific instrument settings.^[24–26] Nordgren *et al.*^[25] reported that when using only one SRM transition for screening urine samples, approximately one-third of their results yielded false positives. This is because either natural and/or synthetic interferents or metabolites found in biofluids can produce both precursor and product ions with *m/z* values exactly the same as those of the substances being analyzed.^[26] For example, cotinine, a metabolite of nicotine which is often detected in urine, has an *m/z* of 176, the same *m/z* ratio as BZP. Although they have the same *m/z* ratio, cotinine does not have an equivalent product ion at *m/z* 91 which is important in terms of possible mistaken identification of BZP use.^[5]

Limit of detection, limit of quantitation, matrix effects, and analyte recovery

The LOD and LOQ were estimated from the lowest calibrator (500 ng/ml) as 3 times the noise value and 10 times the noise value, respectively. The calculated LOQ values were below 30 ng/ml for

all analytes, with the exception of mCPP where the LOQ was estimated at 96 ng/ml (Table 3).

Matrix effects were evaluated following the method described by Matuszewski *et al.*^[12] Samples of the individual analytes were prepared at a concentration of 500 ng/ml in drug-free urine collected from five different sources. The use of more than one source of drug-free matrix is important when investigating the effect of the matrix. Analyzing only one matrix source means that the question of different recoveries in samples from different sources and the potential of matrix effects on analyte quantitation are not dealt with. Analysis of drug-free urine from a number of different sources means that differences are highly likely to appear between samples and an indication of whether sample matrix or differences in sample recovery are likely to affect the basic accuracy and precision of the method.^[12]

Unsurprisingly every analyte suffered from ion suppression (results <100%) or enhancement (results >100%), in the five different sample matrices studied. This is to be expected because the non-selectivity of direct injection means that the appearance of interfering substances, for example, salts, fatty acids, organic bases compete for ionization.^[27] The differences in responses of all the analytes in the five different matrices studied was found to be within \pm 15% (92.6–108%) of the nominal values with the exception of BZP where it was determined to be 75.4% \pm 1.4% (Table 4). It should be noted that the impact of matrix effects on assay performance were evaluated at 500 ng/ml, 50% below the proposed 1000 ng/ml assay cut-off.

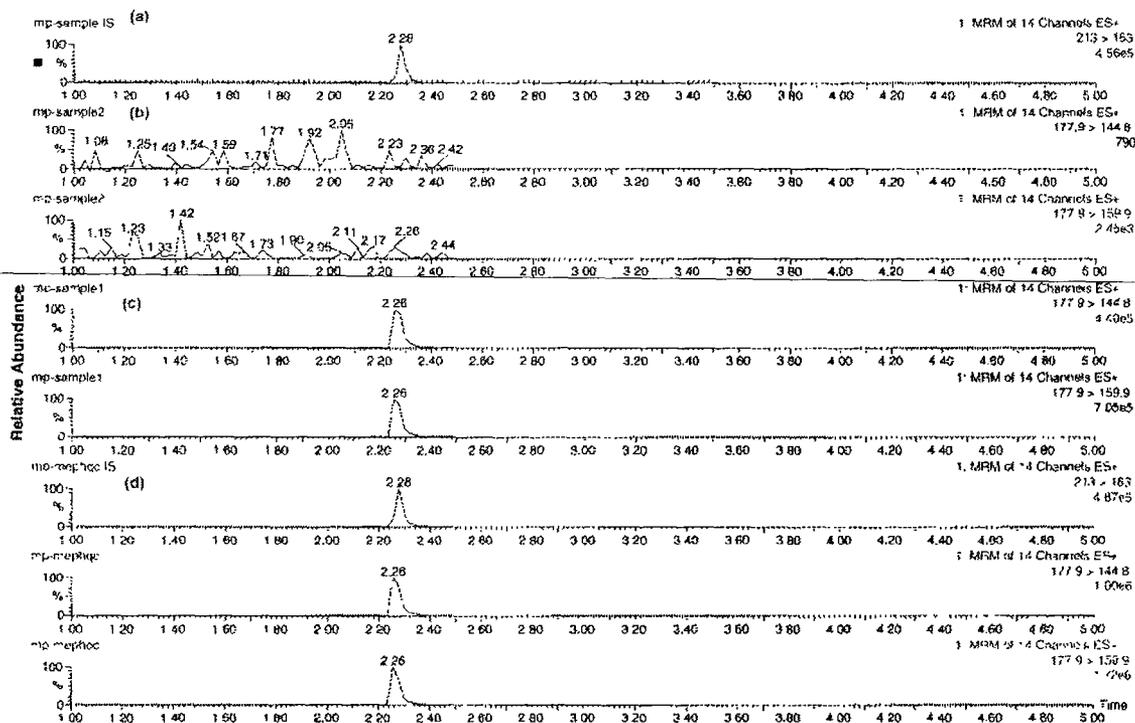


Figure 4. Chromatograms for (A) MDEA-d5 (B) Case sample 2 (C) Case sample 1 (D) QC sample prepared in drug-free urine at a concentration of 1000 ng/ml.

The value of $\pm 15\%$ was proposed as an acceptable limit for matrix effects variability as part of the 2007 American Association of Pharmaceutical Scientists (AAPS)/Food and Drug Administration (FDA) conference report: *Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays*.^[28] The use of these criteria would suggest that an awareness and quantification of matrix effects are more important than automatically trying to eliminate them entirely.^[29] However, when variability is observed outside of the $\pm 15\%$ cut-off value, adjustments should be made to the method where possible in order to reduce the matrix's influence.^[29]

McCauley-Myers *et al.*^[22] state that the success of direct injection is dependent on the combination of analyte, dilution factor, diluents, organic content of the mobile phase, and injection volume. It would also appear that a balance must be found between the dilution factor and the ion suppression or enhancement likely to be encountered. One option which could be investigated to minimize matrix effects is the use of alternative dilution factors. In theory, the more dilute the matrix, the less interferences and impact on the column and/or source. However, it is possible over-dilution may reduce the detection of some analytes due to the LOD of the assay.^[27] The results of this study (Table 3) show that using a 1:4 (v/v) dilution in conjunction with the UPLC-MS/MS parameters described, all compounds could be detected at 500 ng/ml, half that of the chosen assay cut-off, providing a reassuring degree of latitude if instrumental sensitivity decreases prior to routine maintenance.

Analyte recovery appears to be consistently better for the cathinone derivatives ($\sim 93.0\% - \sim 105.3\%$) compared to the piperazine derivatives ($\sim 77.2\% - \sim 88.2\%$), which might suggest they are less stable in the matrix. The fact that BZP, as the earliest eluting substance, has the greatest amount of ion suppression ($75.4\% \pm 1.4\%$) is not surprising. Ion suppression particularly

affects early eluting analytes because when using reverse phase chromatography the most polar analytes elute most quickly.^[30,31] There is little distinction between the unwanted polar interferences and the polar analyte of interest.

Research shows that using alternative LC-MS methods to those used in this study, BZP elutes significantly earlier than other piperazine derivatives and consequently undergoes the most ion suppression.^[3]

Case samples analysis

During the course of this study, two samples were received by the laboratory for mephedrone analysis. Sample one was collected from a known mephedrone user.

The second sample was collected from an individual who was a known associate of the donor of the first sample. Both these samples were analyzed using the method described.

The calibration standards (500 ng/ml, 1000 ng/ml, and 2000 ng/ml) showed good linearity for mephedrone ($r^2 = 0.999$).

Analysis of sample 1 identified the presence of mephedrone. However, this result was reported as negative as the signal intensities of both the target transition ($m/z 177.9 > 144.8$) and the qualifier transition ($m/z 177.9 > 159.9$) were below that of the 1000 ng/ml cut-off (Figure 4). None of the target analytes were identified in sample 2.

Conclusions and future direction

The results of this study support previously published research which suggests that drug-testing laboratories will not detect the presence of the emerging designer drugs, for example, β -keto amphetamines and piperazine derivatives using routine

immunochemical screening techniques.^[2,10,14,18,19] Screening by hyphenated mass spectrometry is an obvious way forward with the rapid increase in availability of new psychoactive substances, as the retention time and the *m/z* of ions for each new drug can be quickly incorporated into existing runs. The incorporation of UPLC resulted in an overall analysis time after sample dilution within 5 min/sample. This short analytical run-time, combined with a simple sample preparation procedure allows the method to be adapted for routine workplace drug testing within high sample throughput laboratories.

The primary focus for a workplace drug testing programme, where the main aim is to deter drug misuse amongst the workforce, is the detection of recent drug administration which can be achieved by the detection of parent compounds in urine. For this reason, a relatively high reporting threshold of 1000 ng/ml was chosen. Even though this threshold is considerably higher than the LOD for drugs targeted, it correlates to the amphetamine immunoassay screening threshold currently employed. This threshold contrasts with that of forensic toxicology, where emphasis is placed on much lower reporting thresholds, including the analysis for late eliminating metabolites, often necessitating preliminary sample extraction. The metabolism of designer drugs has been reviewed^[34,35] and, moreover, recent data has been published regarding the metabolism of mephedrone, butylone, methylone, and MDPV.^[36,37] Whether any designer drugs are excreted to such a small extent that they are unlikely to exceed the reporting threshold chosen for workplace testing remains to be evaluated, but the targeting of the major metabolites will then be a logical alternative. In the interim, it seems sensible to add such major metabolites to drug screens to aid such comparison, as and when reference standards for metabolites become available.

It may be possible to develop this method further to achieve greater analytical sensitivity and therefore support its application to selected areas of clinical and forensic investigation. Of particular interest would be to investigate the combination of 'dilute and shoot' in conjunction with high resolution mass spectrometry to aid discrimination of drugs from matrix interferences. Moreover, full-scan accurate MS can give broad coverage of known compounds and the ability to rapidly locate new compounds, as exemplified recently regarding the analysis of cannabinomimetics.^[38]

References

- [1] A Wohlharth, W Weinmann, S Dresen. LC-MS/MS screening method for designer amphetamines, tryptamines and piperazines in serum. *Anal. Bioanal. Chem.* **2010**, *396*, 2403.
- [2] S Pichini, M Pujadas, E Marchei, M Pellegrini, J Fiz, R Pacifici, P Zuccaro, M Farre, R De la Torre. Liquid chromatography-atmospheric pressure ionisation electrospray mass spectrometry determination of 'hallucinogenic designer drugs' in urine of consumers. *J. Pharmacol. Biomed. Anal.* **2008**, *47*, 335.
- [3] R Newcombe. *Mephedrone: the use of mephedrone (m-cat, Meow) in Middlesborough*, Lifeline Publications & Research: Manchester, UK, **2010**.
- [4] M.R Meyer, J Wilhelm, F.T Peters, H.H Maurer. Beta-keto amphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone and methylone in urine using GC-MS. *Anal. Bioanal. Chem.* **2010**, *397*, 1225.
- [5] S.P Vorce, J.M Holler, B Levine, M.R Past. Detection of 1-benzylpiperazine and 1-(3-trifluoromethylphenyl)-piperazine in urine analysis specimens using GC-MS and LC-EI-MS. *J. Anal. Toxicol.* **2008**, *32*, 444.
- [6] M Peat. *Workplace Drug Testing. Clarke's Analysis of Drugs and Poisons*. (Eds: A.C Moffat, M.D Osselton, B Widdop), Pharmaceutical Press: London, UK, **2004**, pp. 68–79.
- [7] D Lane. *Antibodies – A Laboratory Manual*. Cold Spring Harbor Laboratory Press: New York, **1988**, pp 148–149.
- [8] A Kankaanpää, T Gunnar, K Ariniemi, P Lillsunde, S Mykkanen, T Seppala. Single-step procedure for gas chromatography-mass spectrometry screening and quantitative determination of amphetamine-type stimulants and related drugs in blood, serum, oral fluid and urine samples. *J. Chromatogr. B* **2004**, *810*, 57.
- [9] E Gallardo, M Barroso, J.A Queiroz. LC-MS: a powerful tool in workplace drug testing. *Drug Test. Analysis* **2009**, *1*, 109.
- [10] J.C Eichhorst, M.L Etter, N Rousseaux, D.C Lehotay. Drugs of abuse testing by tandem mass spectrometry: a rapid, simple method to replace immunoassays. *J. Clin. Biochem.* **2009**, *42*, 1531.
- [11] R Bonfiglio, R King, T Olah, K Merkle. The effects of sample preparation methods on the variability of the electrospray ionisation response for model drug compounds. *Rapid Commun. Mass Spectrom.* **1999**, *13*, 1175.
- [12] B.K Matuszewski, M.L Constanzer, C.M Chavez-Eng. Strategies for the assessment of matrix effect in quantitative bioanalytical methods based on HPLC-MS/MS. *Anal. Chem.* **2003**, *75*, 3019.
- [13] M Andersson, E Gustavsson, N Stephanson, O Beck. Direct injection LC-MS/MS method for identification and quantification of amphetamine, methamphetamine, 3,4-methylenedioxymphetamine and 3,4-methylenedioxymethamphetamine, in urine drug testing. *J. Chromatogr. B* **2008**, *861*, 22.
- [14] A.A.S Marais, J.B Laurens. Rapid GC-MS confirmation of amphetamines in urine by extractive acylation. *Forensic Sci. Int.* **2009**, *183*, 78.
- [15] B Loo, C Lingenfelter, P Watson, K Tang, D Davoudzadeh. Multiplex assay of amphetamine, methamphetamine and ecstasy drug using CEDIA technology. *J. Anal. Toxicol.* **2002**, *28*, 267.
- [16] R.F Staack, G Fritschi, H.H Maurer. Studies on the metabolism and toxicological detection of the new designer drug *N*-benzylpiperazine in urine in gas chromatography-mass spectrometry. *J. Chromatogr. B* **2002**, *773*, 35.
- [17] EMCDDA, *Drug Profiles: BZP and other piperazines*. Available at: www.emcdda.europa.eu/publications/drug-profiles/bzp [9 May 2010].
- [18] J Button, S Kenyon. Piperazines – the new emerging recreational drugs. Available at: www.iatdmct.org/.../Volume%206_Issue%202_Jun%202006-Piperazines_JB_SK.pdf [11 August 2010].
- [19] D De Boer, I.J Bosman, E Hidvegi, C Manzoni, A.A Benko, L Dos Reys, R Maes. Piperazine-like compounds: a new group of designer drugs-of-abuse on the European market. *Forensic Sci. Int.* **2001**, *121*, 47.
- [20] Advisory Council on the Misuse of Drugs. *Consideration of the Cathinones*, **2010**. Available at: <http://www.homeoffice.gov.uk/publications/drugs/acmd1/acmd-cathinones-report-2010?view=Binary> [10 May 2010].
- [21] T Kraemer, H.H Maurer. Determination of amphetamine, methamphetamine and amphetamine-derived designer drugs or medicaments in blood and urine. *J. Chromatogr. B* **1998**, *713*, 163.
- [22] D.L McCauley-Myers, T.H Eichhold, R.E Bailey, D.J Dobroszi, K.J Best, J.W Hayes II, S.H Hoke II. Rapid bioanalytical determination of dextromethorphan in canine plasma by dilute-and-shoot preparation combined with one minute per sample LC-MS/MS analysis to optimise formulations for drug discovery. *J. Pharm. Biomed. Anal.* **2000**, *23*, 825.
- [23] M Wood, M Laloup, N Samyn, M del Mar Ramirez, R Fernandez, E.A de Bruijn, R.A.A Maes, G De Broek. Recent applications of liquid chromatography-mass spectrometry in forensic science. *J. Chromatogr. A* **2006**, *1130*, 3.
- [24] H.K Nordgren, P Holmgren, P Liljeberg, N Eriksson, O Beck. Application of direct urine LC-MS/MS analysis for screening of novel substances in drug abusers. *J. Anal. Toxicol.* **2005**, *29*, 234.
- [25] F.L Sauvage, J-M Gaulier, G Lachatre, P Marquet. Pitfalls and prevention strategies for Liquid chromatography-tandem mass spectrometry in the selected reaction-monitoring mode for drug analysis. *Clin. Chem.* **2008**, *54*, 1519.
- [26] H.H Maurer. Perspectives of liquid chromatography couple to low- and high-resolution mass spectrometry for screening, identification and quantification of drugs in clinical and forensic toxicology. *Ther. Drug Monit.* **2010**, *32*(3), 324.
- [27] F Badoud, E Grata, L Perrenoud, L Avois, M Saugy, S Rudaz, J-L Veuthey. Fast analysis of doping agents in urine by ultra-high-

- pressure liquid chromatography-quadrupole time-of-flight mass spectrometry screening analysis. *J. Chromatogr. A* **2009**, *1216*, 4423.
- [28] C.T. Viswanathan, S. Bansai, B. Booth, A.J. DeStefano, M.J. ROse, J. Sailstad, V.P. Shah, J.P. Skelly, P.G. Swan, R. Weiner. Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays. *Pharm. Res.* **2007**, *24*, 1962.
- [29] I Marchi, V.Vietter, F.Badoud, M.Fathi, M.Saugy, S.Rudaz, J-L.Veuthey. Characterisation and classification of matrix effects in biological samples analyses. *J. Chromatogr. A* **2010**, *1217*, 4071.
- [30] E. Gustavsson, M. Andersson, N. Stephanson, O. Beck. Validation of direct injection electrospray LC-MS/MS for confirmation of opiates in urine drug testing. *J. Mass Spectrom.* **2007**, *42*, 881.
- [31] H. Mei, Y. Hsieh, C. Nardo, X. Xu, S. Wang, K. Ng, W.A. Korfmacher. Investigation of matrix effects in bioanalytical high-performance liquid chromatography/tandem mass spectrometric assays: application to drug discovery. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 97.
- [32] Advisory Council on the Misuse of Drugs, Methamphetamines Review, **2005**. Available at: <http://www.homeoffice.gov.uk/publications/drugs/acmd1/ACMD-meth-report-November-2005?view=Binary> [10 May 2010].
- [33] A.M. Feyissa, J.P. Kelly. A review of the neuropharmacological properties of khat. *Progress Neuropharmacol. Bio. Psych.* **2008**, *32*, 1147.
- [34] M.R. Meyer, H.H. Maurer. Metabolism of designer drugs of abuse: an updated review. *Curr. Drug Metab.* **2010**, *11*, 468.
- [35] R.F. Staack, H.H. Maurer. Metabolism of designer drugs of abuse. *Curr. Drug Metab.* **2005**, *6*, 259.
- [36] M.R. Meyer, J. Wilhelm, F.T. Peters, H.H. Maurer. Beta-keto amphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone, and methylone in urine using gas chromatography-mass spectrometry. *Anal. Bioanal. Chem.* **2010**, *397*, 1225.
- [37] M.R. Meyer, P. Du, F. Schuster, H.H. Maurer. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-pyrovalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J. Mass Spectrom.* **2010**, *45*, 1426.
- [38] S. Hudson, J. Ramsey, L. King, S. Timbers, S. Maynard, P.J. Dargan, D.M. Wood. Use of high-resolution accurate mass spectrometry to detect reported and previously unreported cannabinomimetics in 'herbal high' products. *J. Anal. Toxicol.* **2010**, *34*, 252.

106

TOXICOLOGY OBSERVATION

Death Following Recreational Use of Designer Drug “Bath Salts” Containing 3,4-Methylenedioxypropylamphetamine (MDPV)

Brittany L. Murray · Christine M. Murphy · Michael C. Beuhler

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Abstract

Introduction 3,4-Methylenedioxypropylamphetamine (MDPV) is a designer stimulant drug that has gained popularity in the USA. Although adverse effects of MDPV have been described, to our knowledge, this is the first reported death.

Case Report We report the case of a 40-year-old male who injected and snorted “bath salts” containing MDPV and subsequently became agitated, aggressive, and experienced a cardiac arrest. He was resuscitated after his initial arrest; however, he developed hyperthermia, rhabdomyolysis, coagulopathy, acidosis, anoxic brain injury, and subsequently died.

Discussion This is the first case in the medical literature to report death due to isolated confirmed MDPV intoxication. The manner of death is also consistent with excited delirium syndrome.

Keywords 3,4-Methylenedioxypropylamphetamine · Bath salts · Excited delirium syndrome · MDPV · Designer drug

Introduction

Psychoactive products containing β -keto phenylalkylamines such as 3,4-methylenedioxypropylamphetamine (MDPV), mephedrone, and methylone have entered the recreational

drug market over the past several years. These products are often labeled as “bath salts” or “plant food,” with the disclaimer that they are “not for human consumption” to skirt state and federal laws. Although states are creating new laws to address these derivatives, an increasing number of exposures have been reported to United States (US) poison centers since late 2010 [1].

MDPV is a ring-substituted analogue of propylamphetamine (Fig. 1). Propylamphetamine is a stimulant and a schedule V ^{CSA} controlled substance that was first synthesized in 1964. The synthesis of MDPV was first reported in 1969 [2, 3]. The chemical structure of MDPV is similar to methcathinone (“Meat”) and to hallucinogenic substances like 3,4-methylenedioxymethamphetamine (MDMA or “Ecstasy”), but it is best characterized as a β -keto phenylalkylamine (Fig. 1). Over the past decade, MDPV has gained popularity as a designer drug, or “legal high,” across Europe. The first designer drug containing MDPV was identified in Germany in 2007 [4]. In Japan, MDPV was retrospectively identified in designer drugs confiscated in the year 2006 [5]. The recreational use of MDPV in the USA has become more prevalent since late 2010 and it is now illegal in many states [1]. We report the first case of isolated recreational use of MDPV resulting in excited delirium syndrome and ultimately death, with confirmatory toxicological analyses.

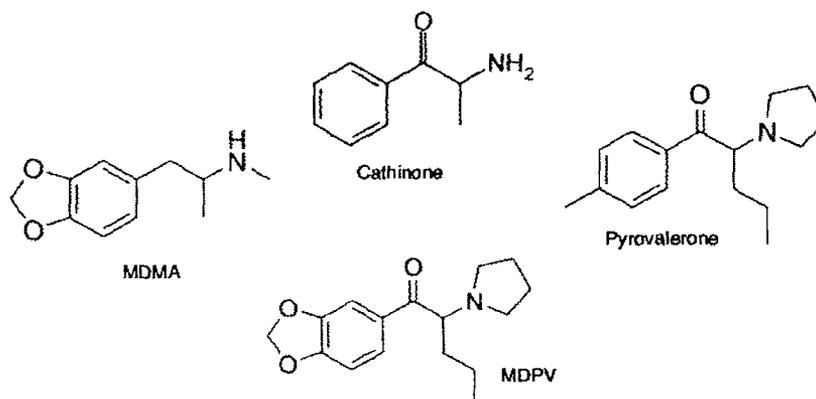
Case Report

A 40-year-old man with a history of bipolar disorder snorted and injected an unknown amount of “bath salts.” Family and friends reported he had recently switched from abusing cocaine to using “bath salts” products. Shortly after his consumption of this product, he became aggressive, uncontrollable, delusional, removed all of his clothing, and

B. L. Murray · C. M. Murphy (✉)
Department of Emergency Medicine, Carolinas Medical Center,
PO Box 32861, MEB 3rd Floor,
Charlotte, NC 28232, USA
e-mail: christine.murphy66@gmail.com

M. C. Beuhler
Carolinas Poison Center,
Charlotte, NC, USA

Fig. 1 Chemical structures of 3,4-methylenedioxypropylvalerone (MDPV); cathinone; 3,4-methylenedioxyamphetamine (MDMA); and pyrovalerone

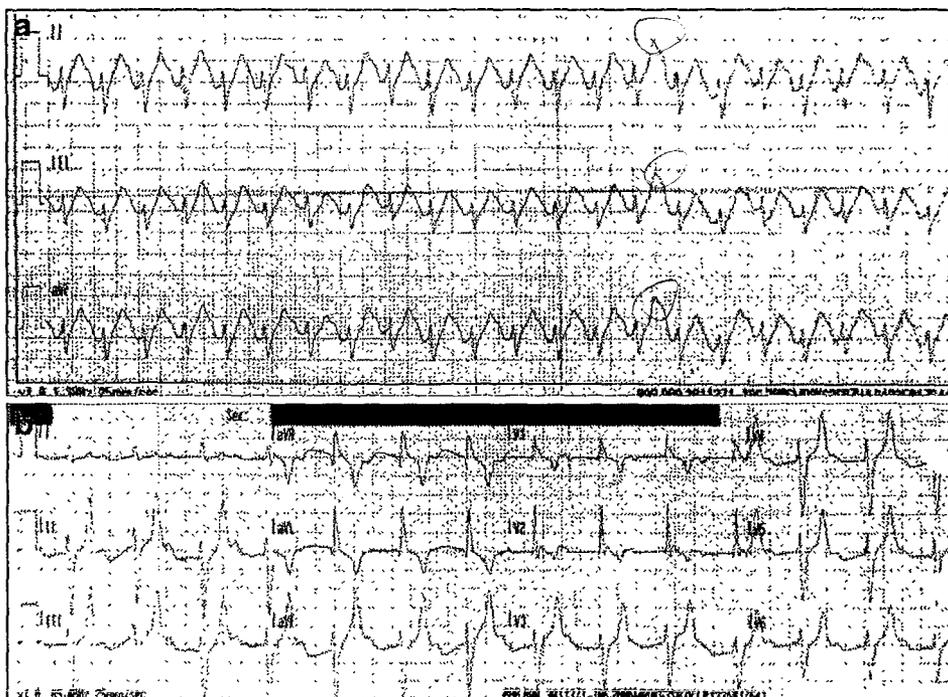


ran outside. Police were called and while being taken into custody, the patient displayed aggression, considerable strength, and violent behavior. An electronic control device was discharged three times in an effort to overpower him and protect others on scene. During ambulance transport, he remained aggressive and delusional and was physically restrained. He was noted to have slightly labored breathing and was placed on a non-rebreather mask (NRB) with 100% oxygen. He was yelling incomprehensibly and was noted to have dilated pupils. Initial vital signs in the prehospital setting were as follows: heart rate 164 beats per minute (bpm); blood pressure 131/72 mmHg; respiratory rate 24 breaths/min, and oxygen saturation of 100% on NRB. Prehospital electrocardiogram (EKG) initially demonstrated sinus tachycardia with widened QTc interval and peaked T waves (Fig. 2a). Repeat EKG 10 min later depicted

normal sinus rhythm with persistent peaked T waves (Fig. 2b). Sedation was attempted unsuccessfully with 2 mg of intramuscular lorazepam.

Upon arrival in the hospital, he continued with very aggressive behavior and incomprehensible screaming. A review of the patient's electronic medical records revealed previous routine medications of quetiapine, methadone, temazepam, and 10/650 mg hydrocodone/acetaminophen. As the patient was never conversant, compliance was not established. Vital signs at the time of his arrival, 15 min after reported EMS vital signs, were as follows: oral temperature 98.0°F; blood pressure 100/64 mmHg; heart rate 91 bpm; respiratory rate 12 breaths/min; and oxygen saturation of 100% on NRB. While being transitioned from the Emergency Medical Services stretcher to a hospital bed, and without further intervention, he became very quiet and withdrawn.

Fig. 2 a Initial prehospital EKG. b Repeat prehospital EKG performed 10 min later demonstrating normal sinus rhythm with rate of 85 bpm, PR interval 110 msec, QRS interval 116 msec, QTc interval 414 msec, and peaked T waves



Within 5 minutes of his arrival to the hospital he developed bradycardia and subsequent cardiac arrest with pulseless electrical activity (PEA). Standard advanced cardiac life support measures were initiated including cardiopulmonary resuscitation and administration of two doses each of 1 mg intravenous (IV) epinephrine and 1 mg IV atropine, as well as 100 mg of IV lidocaine. He was intubated and given both 2 mg IV naloxone and 0.5 mg IV flumazenil without effect. Return of spontaneous circulation was achieved after 30 min of resuscitation. Dopamine and phenylephrine infusions were initiated at rates of 5 mcg/kg/h and 10 mcg/h, respectively, due to persistent hypotension despite a bolus infusion of 2 liters 0.9% normal saline (NS).

Immediately after resuscitation, a rectal temperature was 105.4°F, for which he was given 1,300 mg of acetaminophen per rectum. Other vital signs included a blood pressure of 70/32 mmHg; heart rate of 91 bpm; and oxygen saturation of 100% while mechanically ventilated. Physical examination revealed a Glasgow coma scale score of 3 and pupils dilated at 6 mm with minimal reaction to light. Skin examination revealed dry skin with multiple needle marks in both antecubital fossae. Additionally, there was no evidence of hypertonia, hyperreflexia, inducible or spontaneous clonus, or bruxism.

Pertinent initial labs in the immediate post-arrest period included: potassium of 7.4 mmol/L, creatinine of 3.0 mg/dL, negative serum acetaminophen and ethanol levels (limit of detection less than or equal to 5 mg/dL), a salicylate level of 4.1 mg/dL, and a urine drug screen positive for opiates but negative for cocaine, phencyclidine, amphetamine, tetrahydrocannabinol, benzodiazepines, and barbiturates. Initial international normalized ratio (INR) was 1.01; creatinine

kinase 234 U/L; aspartate aminotransferase (AST) 19 U/L; and alanine transaminase (ALT) was 36 U/L. An EKG was also obtained at this time and showed changes consistent with hyperkalemia (peaked T waves) with a sinus bradycardia at a rate of 56 bpm with a markedly prolonged QRS of 240 milliseconds (msec) (Fig. 3). The patient was then transferred to a tertiary hospital with hemodialysis capabilities and a toxicology consult service.

On arrival to the tertiary care center, the patient's temperature had decreased to 100.2°F without further intervention. The patient's blood pressure remained low at 85/41 mmHg despite elevated doses of dopamine (20 mcg/kg/min), phenylephrine (180 mcg/h), and additional boluses of chilled IV NS (4 liters); therefore, norepinephrine was started (4 mcg/min). His heart rate was 115 bpm and oxygen saturation of 100% with the patient breathing over the set ventilator rate of 20 breaths/min at 32 breaths/min. His pupils remained dilated and were minimally reactive to light; however, on neurologic examination, he had a normal gag reflex, normal corneal reflexes, and he flexed in response to pain with all four extremities. Repeat EKG showed a bradycardia with a rate of 53 bpm, a right bundle branch block with hyperacute T waves, some ST depression in V2 and V3, a QRS interval of 158 msec, and QTc interval of 420 msec. A venous blood gas was performed: pH 7.2, pCO₂ 39 mmHg, pO₂ 35 mmHg, HCO₃ 16.2 mmol/L, base excess -11 mEq/L, and serum lactate of 2.83 mmol/L. Laboratory testing repeated 5 h after initial presentation demonstrated continued hyperkalemia (8.0 mmol/L), an elevated creatinine (3.5 mg/dL), and marked increase in AST (869 U/L), ALT (738 U/L), INR (4.2), and creatinine kinase (14,839 U/L). His hyperkalemia was treated with 1 g of calcium gluconate, 50 mEq of sodium

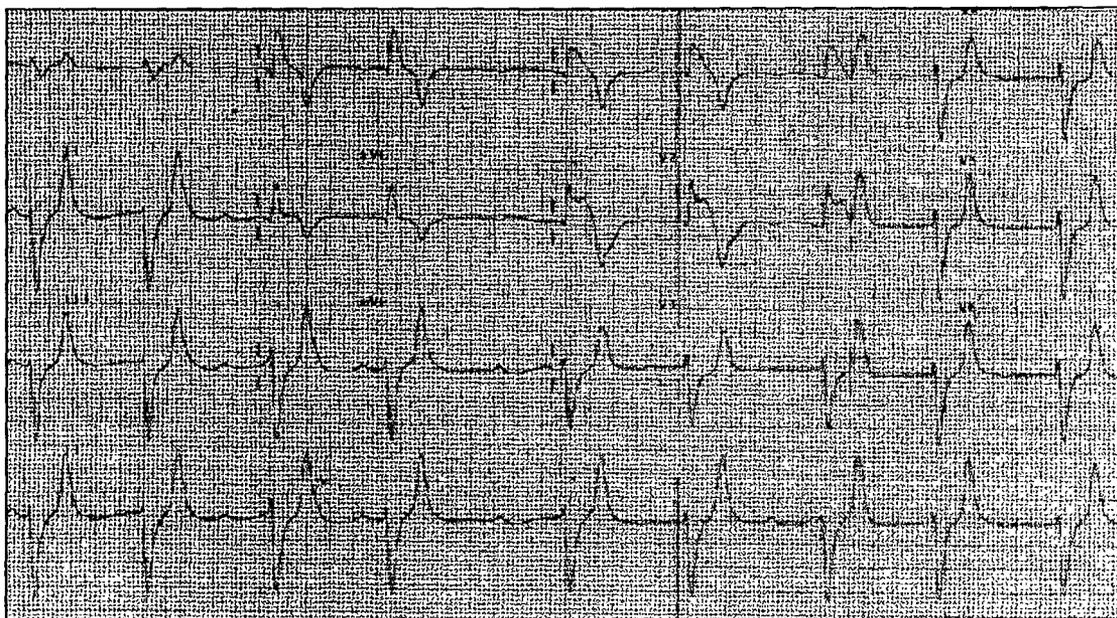


Fig. 3 Post-arrest EKG.

bicarbonate, 10 units of regular insulin, and 50 g of dextrose. His potassium subsequently decreased to 6.0 mmol/L and a repeat EKG demonstrated sinus tachycardia (120 bpm) with normalization of the T waves (Fig. 4).

He was admitted to the medical intensive care unit where he was started on an infusion of 5% dextrose in water with 150 mEq of sodium bicarbonate at a rate of 125 ml/h, hydrocortisone (100 mg IV every 8 h), and propofol infusion (10 mcg/kg/h). Persistent hypotension was treated with an additional 2 liters of bolused NS and a vasopressin infusion was started at 0.04 units/min. Over the next 3 h, he developed a worsening metabolic acidosis (arterial pH 7.14; HCO₃ 10 mmol/L) with oliguric renal failure that progressed to anuria (creatinine 4.26 mg/dL), worsening transaminase elevation (AST 10,873 U/L; ALT 6,623 U/L), and rhabdomyolysis (creatinine kinase 75,952 U/L). His coagulopathy progressed and his INR was >9.3 (upper limit of laboratory detection) and PT >96 s (upper limit of laboratory detection). He was noted to be very pale and began having melanic stools. He developed an anemia (hemoglobin of 6.3 g/dL) and thrombocytopenia with platelets of 11 × 10⁹/L. Hemodialysis was started 17 h after presentation to correct the acidosis and renal failure. Additionally, he received packed red blood cells (4 units), platelets (2 units), cryoprecipitate (9 units), and fresh frozen plasma (10 units). A non-contrasted brain computed tomography showed decreased gray-white matter discrimination interpreted by the radiologist as "likely edema and early anoxic injury." An EEG was performed and showed diffuse slowing consistent with coma and likely anoxic injury.

Despite improvement in his acidosis and anemia after dialysis and transfusion, his neurologic exam worsened. His pupils became fixed and dilated and he lost his

gag, corneal, and vestibulo-ocular reflexes. He no longer responded to noxious stimuli. Approximately 42 h after his initial presentation, the patient was declared brain dead by clinical criteria and support was withdrawn.

During his evaluation, several toxicology laboratories were evaluated on blood and urine samples obtained at the time of arrival to the tertiary care center. His urine was negative for barbiturates, amphetamines, benzodiazepines, cocaine, marijuana, methadone, and opiates. Urine liquid chromatography was positive for trimethoprim. Serum ethanol levels were 11 mg/dL (8 h after presentation) and 25 mg/dL (19 h after presentation). His qualitative urine methadone screen was negative. Serum salicylate level was 7.9 mg/dL and serum acetaminophen level was 2.9 mcg/mL. A lithium level was <0.1 mmol/L. Ethanol, ethylene glycol, methanol, and isopropanol were not detected by gas chromatography 21 h after presentation.

Samples of the patient's urine and serum obtained at the time of his arrival to the tertiary care center were sent for further testing at NMS Labs (Forensic Science Department, Willow Grove, PA). An initial therapeutic drug screen using gas chromatography/mass spectrometry was performed and positive for acetaminophen, caffeine, cotinine, lidocaine, trimethoprim, and MDPV; quetiapine was not detected. Confirmatory testing was undertaken using high performance liquid chromatography/tandem mass spectrometry (LC/MSMS). Specimens were fortified with d₃-MDPV as an internal standard and then subjected to a single step liquid-liquid extraction using trichloroacetic acid (TCA). MDPV was quantified in his urine (670 ng/mL) and serum (82 ng/mL). Trimethoprim was also quantified using high performance thin layer chromatography (12 mcg/mL in urine and 2.2 mcg/mL in serum).

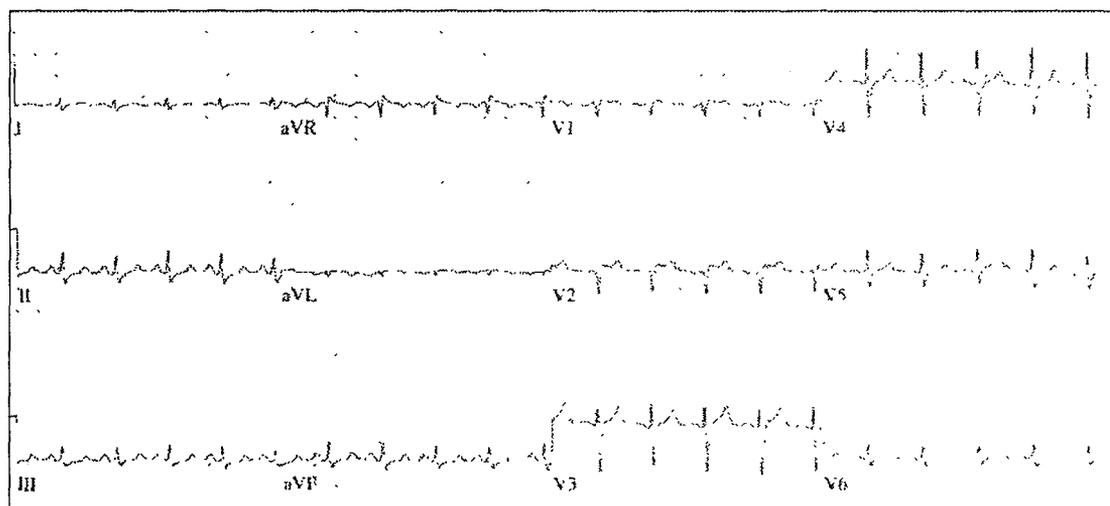


Fig. 4 EKG after treatment for hyperkalemia. PR interval of 125 msec, QRS interval of 83 msec, QTc interval of 412 msec, normalization of the T waves and ST depressions in leads II and III with mild ST elevation in leads V1 and V2

Discussion

MDPV is a white or tan powder that is insufflated, injected intravenously, or ingested. Although few studies have formally examined the clinical effects or metabolism of MDPV in humans, multiple first-hand reports and a handful of published case reports now exist [6–10]. Stimulant effects, an increase in libido, anxiety, hallucinations, and paranoid psychosis have been reported [6]. MDPV appears to undergo CYP450 2D6, 2C19, and COMT phase I metabolism into methylcatechol and pyrrolidine, which in turn are glucuronidated to allow for renal excretion [11, 12]. Although the mechanism of action is not fully elucidated at this time, a dopaminergic mechanism is hypothesized due to the chemical similarity to amphetamines and the behavioral effects of MDPV that mimic those of amphetamines which are known to affect dopaminergic pathways. Studies on other pyrovalerone analogs demonstrated potent inhibition of the dopamine and norepinephrine transporters responsible for reuptake of their corresponding neurotransmitters [13]. Further supporting this hypothesis are animal studies demonstrating MDPV increases dopamine levels in experimental mice and rats [14, 15].

Since late 2010, MDPV has been the most commonly detected β -keto phenylalkylamine in toxicologic analysis of “bath salts,” “plant foods,” or other legal highs in the USA. This differs from the European experience where mephedrone was most commonly detected in these substances [1, 9, 16]. This difference has an unknown clinical significance, as reports of β -keto phenylalkylamine use in the USA describe similar sympathomimetic effects of both mephedrone and MDPV, including agitation, hypertension, palpitations, hallucinations, and violent behavior; however, the US reports have differed in part from those from Europe by the increased prevalence of MDPV, as well as an increase in cases involving rhabdomyolysis.

We report a case of MDPV toxicity with symptoms consistent with Excited Delirium Syndrome (ExDS) followed by a sudden PEA arrest, return of spontaneous circulation, and subsequent development of coagulopathy, rhabdomyolysis, renal failure, hepatic failure, anoxic brain injury, and death. This is the first case in the medical literature to report death due to isolated MDPV intoxication. Toxicological analysis of serum and urine revealed MDPV as an isolated intoxicant. Additionally, while a death consistent with ExDS has been reported after mephedrone use, to our knowledge, this is the first reported MDPV-associated death [17].

ExDS is characterized by delirium with agitation, hyperthermia, tachypnea, tachycardia, a period of “giving up,” or cessation of struggle, followed by cardiac

arrest, as was seen in our patient [18]. ExDS most likely results from dysregulation of dopaminergic pathways. ExDS autopsy data have shown a decreased number of D3 dopamine receptors when compared to controls [19]. This suggests that ExDS patients may lack normal compensatory measures for dealing with rapid changes in dopamine levels. Furthermore, hypothalamic dopamine receptors are responsible for thermoregulation, and patients with ExDS have elevated heat shock proteins consistent with the clinically observed hyperthermia [19]. Hyperthermia in these patients is likely a sign of autonomic dysfunction that results in death in many ExDS patients. However, in patients that survive the initial arrest, such as the patient in this report, hyperthermia likely contributes to the coagulopathy, rhabdomyolysis, and multisystem organ failure that result in death after the initial insult. ExDS has been described with MDMA, cocaine, and amphetamine intoxication [20, 21].

In our case, the patient's previous history of cocaine abuse may have also predisposed him to ExDS, as chronic cocaine abuse is known to alter neurotransmitters such as dopamine [22]. The dopaminergic effects of MDPV likely contributed to aberrant thermoregulation, and the sympathomimetic effects contributed to the agitation, delirium, and the cardiac arrest in this patient. Treatment for MDPV intoxication, along with other drugs in the stimulant class and patients with ExDS remains largely supportive, with the use of intravenous benzodiazepines, intravenous fluids, and cooling.

The patient in this case was also found to have trimethoprim present on serum and urine testing. This was quantified (12 mcg/mL in urine and 2.2 mcg/mL in serum) and present in amounts that exceed previous reports of peak plasma levels in single one-time ingestions of 160 mg doses [23]. Trimethoprim is not reported to cause stimulant effects with chronic use or in acute overdose. There are reports of hyperkalemia occurring in patients predisposed to potassium retention (underlying renal failure or concurrent diuretic use) [24, 25]. Our patient was not known to be taking a trimethoprim-containing medication, and personal communication with the laboratory performing the test (telephone correspondence with Dr. S. Kacinko, NMS Labs, August 2011) revealed an additional case where MDPV and trimethoprim were found together using similar testing methods. We hypothesize that this may be an adulterant in some formulations of “bath salts,” including that which our patient consumed. It is therefore possible trimethoprim contributed to our patient's hyperkalemia, but we do not feel it is responsible for his ExDS symptoms or ultimate death.

We were initially perplexed as to why our patient's serum ethanol level continued to rise well after admission even with the initiation of hemodialysis; however, ethanol

was not detected on a volatile alcohol screen performed on blood obtained during this time period. Most likely the serum ethanol levels quantified via the serum ethanol assay (Beckman UniCel Dx C, Beckman Coulter Inc, Brea, CA) were falsely elevated due to interference from the patient's profoundly elevated lactate dehydrogenase (LDH) (11,108 IU/L, 19 h after presentation) and lactate levels (10.7 mmol/L, 19 h after presentation). This interference of LDH and lactate with serum ethanol determination has been described with multiple instruments/assays, including the methodology used to measure ethanol in this case [26–28]. These assays are based on the conversion of ethanol to acetaldehyde by alcohol dehydrogenase reducing NAD to NADH in the process, which is quantitated by absorbance at 340 nm due to NADH formation. Assay interference occurs when excess LDH and lactate allow for conversion of NAD to NADH in a reaction unrelated to the presence of ethanol.

Conclusion

Recreational abuse of “bath salts” products continues despite legislative initiatives to prohibit its use. While this is the first reported case of death due to isolated recreational use of MDPV with confirmatory toxicological analyses, further characterization of symptoms related to intoxication and associated deaths is needed. This case highlights the need for emergency physicians and toxicologists to be vigilant in testing for novel drugs of abuse, as it allows for an improved understanding of the potential toxicity of these drugs and associated adulterants.

References

- Spiller H, Ryan M, Weston R, Jansen J (2011) Clinical experience with and analytical confirmation of “bath salts” and “legal highs” (synthetic cathinones) in the United States. *Clin Toxicol* 49(6):499–505
- Yohannan J, Bozenko J (2010) The characterization of 3, 4-methylenedioxypropylvalerone (MDVP). *Microgram Journal* 7:21–15
- 1-[(3, 4-Methylenedioxy)phenyl]-2-pyrrolidino-1 alkanones as stimulants (1969) *Boehringer Ingelheim Study*
- Westphal F, Junge T, Rösner P, Sönnichsen F, Schuster F (2009) Mass and NMR spectroscopic characterization of 3,4-methylenedioxypropylvalerone: a designer drug with alpha-pyrrolidinophenone structure. *Forensic Sci Int* 190(1–3):1–8
- Uchiyama N, Kikura-Hanajiri R, Kawahara N, Goda Y (2008) Analysis of designer drugs detected in the products purchased in fiscal year 2006. *Yakugaku Zasshi* 128(10):1499–1505
- Antonowicz J, Metzger A, Ramanujam S (2011) Paranoid psychosis induced by consumption of methylenedioxypropylvalerone: two cases. *Gen Hosp Psychiatry* 33(6):640.e5–6
- Penders T, Gestring R (2011) Hallucinatory delirium following use of MDPV: “Bath Salts.” *Gen Hosp Psychiatry* 30:525–526
- Kriikku P, Wilhelm L, Schwarz O, Rintatalo J (2011) New designer drug of abuse: 3,4-methylenedioxypropylvalerone (MDPV) findings from apprehended drivers in Finland. *Forensic Sci Int* 210(1–3):195–200
- Centers for Disease Control and Prevention (CDC) (2011) Emergency department visits after use of a drug sold as “bath salts”—Michigan, November 13, 2010–March 31, 2011. *MMWR Morb Mortal Wkly Rep* 60(19):624–627
- Smith C, Cardile C, Miller C (2011) Bath salts as a “legal high.” *Am J Med*. doi:10.1016/j.amjmed.2011.03.014
- Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F (2010) Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom* 24(18):2706–2714
- Meyer M, Du P, Schuster F, Maurer H (2010) Studies on the metabolism of the α -pyrrolidinophenone designer drug methylenedioxy-propylvalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom* 45(12):1426–1442
- Meltzer P, Butler D, Deschamps J, Madras B (2006) 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogs A promising class of monoamine uptake inhibitors. *J Med Chem* 49(4):1420–1432
- Fuma T, Kodama T, Honda Y, Tanaka T, Kubo Y, Ohashi N et al (2009) Influence of methylenedioxypropylvalerone on central nervous system using micro dialysis method. *ChemBio Integrated Management* 5:62–72
- Nagai F et al (2007) The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. *Eur J Pharmacol* 559(2–3):132–137
- McElrath K, O'Neill C (2011) Experiences with mephedrone pre- and post-legislative controls: perceptions of safety and sources of supply. *Int J Drug Policy* 22(2):120–127
- Lusthof KJ, Oostinga R, Maesa A, Verschraagen M, Dijkhuizen A, Sprong AGA (2011) A case of extreme agitation and death after the use of mephedrone in the Netherlands. *Forensic Sci Int* 206(1–3):e93–e95
- Takeuchi AT, Henderson S (2011) Excited delirium. *West J Emerg Med* 12(1):77–83
- Mash D, Duque L, Pablo J, Qin Y, Adi N, Hearn W, Hyma B, Karch S, Druid H, Wetli C (2009) Brain biomarkers for identifying excited delirium as a cause of sudden death. *Forensic Sci Int* 190(1–3):e13–e19
- Dar K, McBrien M (1996) MDMA induced hyperthermia: report of a fatality and review of current therapy. *Intensive Care Med* 22(9):995–996
- DiMaio TG, DiMaio VJ (2005) Excited delirium syndrome: cause of death and prevention. CRC Press, New York
- Staley J, Welti C, Rutenber A et al (1995) Altered dopaminergic synaptic markers in cocaine psychosis and sudden death. *NIDA Res Monogr Series* 153:491
- Bach MC, Gold O, Finland M (1973) Absorption and urinary excretion of trimethoprim, sulfamethoxazole and trimethoprim-sulfamethoxazole. *J Infect Dis* 128(Suppl):584–598

24. Weir M, Juurlink D, Gomes T, Mamdani M, Hackam D, Jain A et al (2010) Beta-blockers, trimethoprim-sulfamethoxazole, and the risk of hyperkalemia in the elderly: a nested case-control study. *Clin J Am Soc Nephrol* 5:1544–1551
25. Lam N, Weir M, Juurlink D, Gunraj N, Gomes T, Mamdani M et al (2011) Hospital admissions for hyperkalemia with trimethoprim-sulfamethoxazole: a cohort study using health care database codes for 393,039 older women with urinary tract infections. *Am J Kidney Dis* 57(3):521–523
26. Nine J, Moraca M, Virji M, Rao K (1995) Serum-ethanol determination: comparison of lactate and lactate dehydrogenase interference in three enzymatic assays. *J Anal Toxicol* 19:192–196
27. Gharapetian A, Holmes D, Urquhart N, Rosenerg F (2008) Dehydrogenase interference with enzymatic ethanol assays: forgotten but not gone. *Clin Chem* 54(7):1251–1252
28. King G, Bissell M (2011) Does your lab produce false positive ethanol results? AACC/CAP Serum Alcohol Proficiency Survey A12-C:2–4

67

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POISONS CENTRE

Clinical experience with and analytical confirmation of “bath salts” and “legal highs” (synthetic cathinones) in the United States

HENRY A. SPILLER¹, MARK L. RYAN², ROBERT G. WESTON³, and JOANNE JANSEN⁴

¹Kentucky Regional Poison Center, Louisville, KY, USA

²Louisiana Poison Center, Shreveport, LA, USA

³Oklahoma State Bureau of Investigation, Edmond, OK, USA

⁴Sullivan University, College of Pharmacy, Louisville, KY, USA

Recently, there has been a worldwide rise in the popularity and abuse of synthetic cathinones. In 2009 and 2010, a significant rise in the abuse of a new group of synthetic cathinones was reported in Western Europe. In 2010, the rapid emergence of a new drug of abuse, referred to as bath salts or “legal high,” occurred in the USA. The growing number of cases along with the alarming severity of the effects caused by the abuse of these substances prompted significant concern from both healthcare providers and legal authorities. We report the experience of the first 8 months of two regional poison centers after the emergence of a new group of substances of abuse. *Method.* This was a retrospective case series of patients reported to two poison centers with exposures to bath salts. Additionally, 15 “product samples” were obtained and analyzed for drug content using GC/MS. *Results.* There were 236 patients of which 184 (78%) were male. Age range was 16–64 years (mean 29 years, SD 9.4). All cases were intentional abuse. There were 37 separate “brand” names identified. Clinical effects were primarily neurological and cardiovascular and included: agitation (n = 194), combative behavior (n = 134), tachycardia (n = 132), hallucinations (n = 94), paranoia (n = 86), confusion (n = 83), chest pain (n = 40), myoclonus (n = 45), hypertension (n = 41), mydriasis (n = 31), CPK elevations (n = 22), hypokalemia (n = 10), and blurred vision (n = 7). Severe medical outcomes included death (n = 1), major (n = 8), and moderate (n = 130). Therapies included benzodiazepines (n = 125), antipsychotics (n = 47), and propofol (n = 10). Primary dispositions of patients were: 116 (49%) treated and released from ED, 50 (21%) admitted to critical care, 29 (12%) admitted to psych, and 28 (12%) lost to follow up. Nineteen patients had blood and/or urine analyzed using GC/MS. MDPV was detected in 13 of 17 live patients (range 24–241 ng/mL, mean 58 ng/mL). The four samples with no drug detected, reported last use of bath salts >20 h prior to presentation. Three of five patients had MDPV detected in urine (range 34–1386 ng/mL, mean 856 ng/mL). No mephedrone or methylene was detected in any sample. Quantitative analysis performed on postmortem samples detected MDPV in blood at 170 ng/mL and in urine at 1400 ng/mL. No other synthetic cathinones were detected. *Discussion.* This is the first report of MDPV exposures with quantitative blood level confirmation. Clinical effects displayed a sympathomimetic syndrome, including psychotic episodes often requiring sedation, movement disorders, and tachycardia. Within 8 months of their appearance, 16 states had added synthetic cathinones to the controlled substances list as a Schedule I drug. *Conclusion.* We report the emergence of a new group of substances of abuse in the USA, known as bath salts, with quantitative results in 18 patients. State and federal authorities used timely information from poison centers on the bath salt outbreak during investigations to help track the extent of use and the effects occurring from these new drugs. Close collaboration between state authorities and poison centers enhanced a rapid response, including legislation.

Keywords Synthetic cathinone; Designer drugs; Stimulants; Sympathomimetic syndrome; Drugs of abuse

Introduction

Recently, there has been a worldwide rise in the popularity and abuse of synthetic cathinones. Abuse of one synthetic cathinone – methcathinone – occurred for several decades in the former Soviet Union, Russia, and Eastern Europe and spread to the West in the 1990s.^{1–3} Methcathinone report-

edly had been developed in the former Soviet Union as an antidepressant in the 1930s and separately developed in the West in the 1950s as an appetite suppressant, but was never marketed due to its strong addictive potential. In 2009 and 2010, a significant rise in the abuse of a new group of synthetic cathinones was reported in Western Europe.^{4–11} In 2010, the first cases of exposure to products marketed as “legal highs” and bath salts were reported to US poison centers. Based on the increased use in Europe and availability on the Internet for similar “legal highs,” these products were believed to contain various synthetic cathinones, including mephedrone (4-methylenemethcathinone), MDPV

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Address correspondence to Henry A. Spiller, MS, DABAT, FAACT, Kentucky Regional Poison Center, PO Box 35070, Louisville, KY 40232-5070, USA. E-mail: henry.spiller@nortonhealthcare.org

(methylenedioxypropylone), methylone (3,4-methylenedioxy-n-methylcathinone), methedrone (4-methoxymethylcathinone), and fluoromethylcathinone.^{12,13} The product packages were labeled as bath salts, insect repellants, stain removers, and plant food. However, the users of these products openly spoke of using them as “legal methamphetamine” or “legal cocaine.” The product labels did not provide any indication of the true active ingredients. Unlike the European experience, where many of the products were being purchased from a “dealer” or over the Internet, in the USA the majority of the new “bath salt” products were being purchased locally in small independent stores, such as gas stations, smoke shops, and “head shops.” The growing number of cases along with the alarming severity of the effects caused by the abuse of these substances prompted significant concern from both healthcare providers and legal authorities. During this period in 2010, there was limited information about what these “products” actually contained or the clinical effects that would be expected from abuse of these substances. We report the experience of the first 8 months of two regional poison centers after the emergence of a new group of substances of abuse.

Methods

A retrospective search was performed at two poison centers for all records involving what came to be known as bath salts, for the period January 2010 through February 2011. An initial search was performed to locate any case with a substance name listed as bath salts, insect repellent, stain remover, plant food, MDPV, mephedrone, methylone, cathinones, white lightning, zoom, blue silk, red dove, ivory wave, white cloud, cloud 9, cloud 10, dynamite, or unknown drug. Poison center case notes were then reviewed to verify if there was documentation that the substances involved an illicit “bath salt” case. In November 2010, both poison centers had agreed to code all these exposures under the term “bath salts”. Product names and descriptions were obtained from the documentation in the case notes. Both centers utilize the electronic medical record system *Toxicall*, which allows review of the record stripped of personal identifiers. All charts were then reviewed by the investigators to verify the substance from the case notes. Calls were received from both the general public and hospitals/healthcare facilities. *Toxicall* allows storage of all calls and consultations on a specific patient in a single medical record, so that each case involved in this study was included only once, despite multiple calls and consultations of many of these patients. Data obtained included age, gender, substance involved, reason for exposure, history of use if obtained, clinical effects, pertinent laboratory values, therapies administered, and medical outcome. Medical outcome designation was the standard American Association of Poison Control Center categories utilized by poison centers.¹⁴ In a number of cases, because of the confused, agitated, or delusional mental state of the patient, the history of use and any previous abuse history were obtained from significant others of the patient.

During December 2010, because of the lack of information on the contents of these new “products,” 15 products in

their sealed original containers were obtained from separate commercial locations (stores) in the two states for analysis of content.

Blood/serum and/or urine waste samples were obtained from 18 patients for analysis as an initial effort to discover what substances might be involved in the toxidrome displayed by the patients. This was part of a public health response to what was considered as an outbreak of a newly emergent substance of abuse. All samples were obtained during initial patient presentation and examination in the emergency department and were obtained after initial clinical use (if any) had been performed.

Chemicals and reagents

Analytical reference standards for MDPV, mephedrone, methylcathinone, and phencyclidine (the latter two used for internal standards) were obtained from Cerilliant. MDPV was received as the powdered HCl salt. A 1 mg/mL (calculated as the free base) stock solution was prepared from this solution by dissolving 11.3 mg MDPV HCl in 10 mL DI water. Mephedrone, methylcathinone, and phencyclidine were received as 1 mg/mL solutions. Blank blood was donated by a local blood bank and determined to be drug free by GC/MS analysis.

Analysis of purchased products

After dissolution in methanol, the products were each analyzed using an Agilent 7890A gas chromatograph coupled to an Agilent 5975C mass spectrometer. The column was an Agilent DB-1 (100% dimethylpolysiloxane) (12 m × 0.2 mm × 0.33 μm). Ultra-pure helium was used as the mobile phase using a constant flow of 0.80 mL/min. Other instrumental parameters included: 1 μL injection, split ratio 300:1, injection port 290°C, oven program 100°C for 15 sec, ramped at 65°C/min to 220°C, then at 40°C to 290 with a final hold time of 6.15 min. The total analysis time was 10 min. The mass spectrometer was programmed with a transfer line temperature of 290°C, source temperature of 230°C, quadrupole temperature of 150°C, solvent delay of 0.85 min, and was operated in scan mode from 50 to 550 m/z for the duration of data collection. Identification of the substances present in the bath salts was determined by retention time and mass spectral comparison of the GC/MS data to known standards.

Quantitation of biological specimens

For the quantitation of the bath salt drugs in biological specimens, methylcathinone and phencyclidine were used as internal standards. The internal standard solution was made by combining 25 μL aliquots of the 1 mg/mL methylcathinone and phencyclidine standards and diluting to 25 mL with DI water, resulting in a 1 μg/mL solution for each drug. Similarly, a 1 μg/mL solution containing both mephedrone and MDPV was prepared by diluting 25 μL of each of the 1 mg/mL solutions to 25 mL DI water.

Mephedrone and MDPV calibrators with concentrations of 25, 50, 75, 100, and 150 ng/mL were prepared by pipetting

appropriate volumes of 1 µg/mL solution into 1 mL aliquots of blank blood obtained from a local blood bank and determined to be drug free by GC/MS analysis.

Sample preparation

The calibrators, 1 mL aliquots of biological specimens, and a 1 mL aliquot of blank blood were pipetted into culture tubes and then extracted using the following procedure. Internal standard (50 µL) was added to each sample, followed by 1 mL of borate buffer. After briefly mixing the samples by vortex, 4 mL of n-butyl chloride was added to each sample. Each tube was capped and shaken for 2 min, followed by centrifugation at 3000 rpm for 3 min. After transferring the resulting organic layer to a 5-mL conical centrifuge tube, 2 mL of 1.0 N HCl was added. The conical tubes were capped and placed on a rotary extractor for 15 min, followed by another 3 min centrifugation at 3000 rpm. The organic layer was discarded. Seven drops (approximately 350 µL) of conc. NH₄OH was added to each to basify the aqueous solution. Chloroform (75 µL) was added, and the samples were capped, shaken for 2 min, and centrifuged again at 3000 rpm for 3 min. The resultant chloroform layer was transferred into autosampler vials and then analyzed by GC/MS.

Analysis

Determination of blood concentration and/or urine concentration was performed using another Agilent 7890A/5975C GC/MS. This instrument was equipped with a DB-1 column having dimensions of 30 m × 0.320 mm × 0.25 µm. For biological samples, 2 µL of extract was injected in splitless mode. Other instrumental parameters: injection port 250°C, ultra-pure helium column flow 1.788 mL/min, oven initial temperature 60°C for 1 min, then 15°C/min ramp to 300°C with a hold time of 3 min, total run time 20 min. The mass spectrometer transfer line, source, and quadrupole temperatures were 280, 230, and 150°C, respectively. The mass spectrometer scanned from 40 to 400 m/z after a solvent delay of 3 min.

Results

The first case was reported in August 2010 in Kentucky and the first case in Louisiana occurred in September 2010. From August 2010 through February 2011, there were 236 patients with a rapid escalation in the number patients reported after November 2010 (see Fig. 1). The majority of patients (n = 184, 78%) were male. The age range was from 16 to 64 years (mean 29 years, SD 9.4). All cases reported the reason for exposure as intentional abuse. Where history was available, a large number of cases reported previous abuse of methamphetamine and/or cocaine and the use of bath salts as a “legal” replacement for these substances. Results from qualitative urine drug screens were recorded in 44 patients and detected positive results for amphetamines, barbiturates, benzodiazepines, caffeine, cannabinoids, cocaine, MDMA, methadone, opiates, oxycodone, and oxymorphone. There were 39 separate “brand” names identified from patient histories (Table 1). In 72% of cases, the originating contact

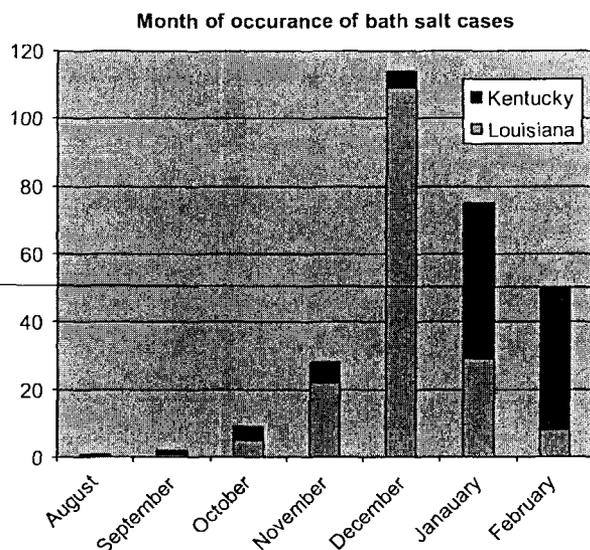


Fig. 1. Month of occurrence of synthetic cathinone cases by state (see colour version of this figure online).

call was from the hospital, with 6% originating from EMS/ambulance service and 22% from the public.

Clinical effects were primarily neurological and cardiovascular and are reported in Table 2. Severe medical outcomes included: death (n = 1), major (n = 8), and moderate (n = 130). The single fatality occurred in a 21-year-old male from a self-inflicted gunshot after an active delusional episode witnessed by family members. A number of alarming and dangerous behaviors (to either self or others) were reported in these patients in temporal association with acute use of large amounts or prolonged use of “bath salts” over several days to several weeks. Examples of these new onset behaviors in separate patients included: jumping out of a window to flee from non-existent pursuers; requiring electrical shock (Taser) and eight responders to initially subdue the patient; repeatedly firing guns out of the house windows at “strangers” who were not there; walking into a river in January to look for a friend who was not there; leaving a 2-year-old daughter in the middle of a highway because she had demons; climbing into the attic of the home with a gun to kill demons that were hiding there, and breaking all the windows in a house and wandering barefoot through the broken glass.

Therapies were primarily sedation and treatment for persistent myoclonus and included the benzodiazepines diazepam, lorazepam, and/or midazolam (n = 125, 53%), the antipsychotics haloperidol and ziprasidone (n = 47, 20%), propofol (n = 10, 4%), and diphenhydramine (n = 2, 1%). The dispositions of patients were: 116 (49%) treated and released from the emergency department, 50 (21%) admitted to a critical care unit, 29 (12%) admitted to behavioral health/psychiatry, 28 (12%) were lost to follow up, and 13 (6%) were managed at a non-healthcare facility.

Eighteen live patients had blood and/or urine analyzed using GC/MS. MDPV was detected in the blood/serum of 13 of 17 patients (range 24–241 ng/mL, mean 58 ng/mL).

Table 1. Names of products reported by users.

Product name	Frequency of reports
Artic blasting station	1
Atomic	1
Bayou revitalisant	1
Blaze	1
Blitz	2
Blue moon	1
Blue silk	5
Bohemian bath salts	2
Bolivian bath salts	2
Dr. booga shooga	3
Cloud 9	73
Cloud 10	2
Columbian odorizer	1
Cotton cloud	4
Dream	1
Dynamite	1
Euphoria	1
Hurricane charlie	1
Ivory wave	9
Ivory wave ultra	1
Kush blitz	1
Lady bubbles	2
Legal	2
Love potion 69	2
Moon dust	4
Night cap	1
NRG-1	1
Q concentrated	1
Red dove	1
Resin	1
Scar face	1
Serenity	1
Super clean stain remover	1
White cloud	1
White diamonds	2
White dove	1
White girls bath salts	1
White lightening	24
Zoom	6

The four samples with no synthetic cathinone detected, reported last use of bath salts >20 h prior to presentation. Additional drugs detected in the blood/serum included citalopram, diazepam, diphenhydramine, hydrocodone, and zolpidem. Three of five patients had MDPV detected in urine (range 34–1386 ng/mL, mean 856 ng/mL). Additional drugs detected in the urine were alprazolam, citalopram, diphenhydramine, hydrocodone, and methamphetamine. No mephedrone or methylone was detected in any sample. Ethanol detection was not included in analysis. Quantitative analysis was performed on postmortem samples in the single fatality. MDPV was detected in blood at 170 ng/mL and in urine at 1400 ng/mL. No other synthetic cathinones were detected.

Fifteen products in their sealed original containers were obtained from separate locations in the two states. The products contained one or more of three of the known synthetic cathinones: 4-methylmethcathinone (mephedrone), methylenedioxypropiovalerone (MDPV), or 4-methylenedioxy-N-methylcathinone

(methylone). Additional substances found included caffeine and an unidentified substance (see Table 3).

Discussion

We report the largest series of synthetic cathinone exposures with a number of important features, including a high incidence of new onset severe neurological/psychiatric changes; qualitative results of the contents of “bath salts”; and quantitative results of blood and urine in synthetic cathinone users.

Previous reports of synthetic cathinone use/abuse have focused primarily on mephedrone and have reported clinical effects consistent with a sympathomimetic syndrome, including tachycardia, agitation, hypertension, palpitations, chest pain, confusion, paranoia, hallucinations, violent behavior, and seizure.^{4-6,8} Our results are consistent with these previous reports. However, in our case series, we found aggressive violent behavior, hallucinations, and paranoia in higher percentages than previously reported. It is interesting to note that the high incidence of neurological/psychiatric changes occurred in a population that had pre-existing experience in illicit stimulant abuse, such as cocaine and methamphetamine, who had not previously reported episodes of neurological/psychiatric changes of such severity. The increased incidence may have occurred for a number of reasons. Experience with misuse/abuse of this drug is limited. While the reported incidence pattern is different from previous reports of synthetic cathinone abuse, the clinical effects reported are similar, and this may simply be a reflection of a difference in dosing patterns or patient populations (e.g. “club” drug use vs. street drug abuse). Another possibility is that this may represent a difference in clinical patterns from the individual synthetic cathinones, perhaps based on subtle differences in the effects on neurotransmitters.¹⁵⁻¹⁷ The previous reports from the European experience primarily involved mephedrone. However, in our case series, all verified serum or urine samples contained MDPV, with no detected mephedrone or methylone. This second possibility should be viewed with caution as only 6% of patients in our series had laboratory verification of their exposure. Movement disorders may also be a differentiating factor. A previously unreported finding in our series was myoclonus in 19% of the patients and elevated CPK in 9% of the patients. One report of “ivory wave” exposure, which may have involved MDPV, reported involuntary facial contortions, supporting a possible movement disorder as a clinical effect with MDPV abuse.¹⁸ Previous reports of a parkinsonian syndrome associated with methcathinone have been attributed to a manganese contamination during illicit preparation of the drug.^{1,2}

Analysis of the “legal high” or “bath salt” products revealed a combination of three synthetic cathinones: mephedrone, methylone, and MDPV. This is similar to the European experience, with some differences.^{12,19} In the USA, the primary synthetic cathinone available was not mephedrone, and the main distribution point was through small local stores. We believe that the wide availability, coupled with the ease of anonymous local purchase and inexpensive

Table 2. Reported clinical effects.

Clinical effect	No. of patients with reported effect (% of total patient group)	Comments
Agitation	194 (82%)	
Combative violent behavior	134 (57%)	
Tachycardia	132 (56%)	Mean heart rate for those with reported tachycardia was 124 (SD 15.5) with a range of 100–178 beats per minute
Hallucinations	94 (40%)	
Paranoia	86 (36%)	
Confusion	83 (34%)	
Myoclonus	45 (19%)	
Hypertension	41 (17%)	
Chest pain	40 (17%)	
Mydriasis	31 (13%)	
CPK elevations	22 (9%)	Mean reported CPK elevation was 1825 U/L with a range of 301–4400 U/L
Hypokalemia	10 (4%)	Mean reported potassium for those with hypokalemia was 2.9 mEq/L with a range of 2.1–3.4 mEq/L
Blurred vision	7 (3%)	
Catatonia	1 (1%)	

Definitions: Tachycardia was a heart rate >99 bpm; hypertension was systolic pressure >170 mmHg or diastolic pressure >90 mmHg; hypokalemia K <3.5 mEq/L, CK elevation CPK >250 U/L.

products, allowed a rapid expansion of these drugs into the market. In many cases, they were easier to obtain than beer or cigarettes. Additionally, no ingredients were listed on the packaging. Unlike web sites that may allude to ingredients that the knowledgeable prospective customer might recognize and/or desire, the bath salt products were primarily sold in small stores by clerks with little or no knowledge of what the product might contain. Analysis of two “brand names” (white lightening and dynamite), which were obtained at different locations, revealed different synthetic cathinones as the primary ingredient, despite similar appearing packaging. The 15 products analyzed and reported here were purchased in December 2010 and may not represent the psychoactive substances in future “bath salt” or “legal high” products. A wide variety of novel psychoactive substances are available and may replace the substances detected in the present group of products.^{12,24}

Quantitative analysis showed serum levels of 24–241 ng/mL of MPV. Previous serum MDPV concentrations in live patients have not been reported, but these concentrations are in the range of the mephedrone level (0.15 mg/L) reported by Wood et al.²⁰ A limitation of interpreting these blood/serum levels of MDPV is that the time from use of the drug to the time of obtaining the sample is not known. We believe this is the first report of postmortem quantitative MDPV concentrations. Postmortem concentrations in five fatalities associated with another synthetic cathinone, mephedrone, ranged from 0.13 to 5.1 mg/L.^{4,5} Urine concentrations after abuse of MDPV have recently been reported in Finland in a group of opioid-dependent patients undergoing opioid substitution therapy.²¹ The similarities between our patient group and the report by Ojanpera et al. were the reported use of MDPV as a substitute for illicit amphetamine and similar urine concentrations. This suggests that urine may be a useful medium to detect previous MDPV abuse.

Table 3. Ingredients detected in “bath salt” samples.

Product name	Drug found	Labeled “use”	Physical appearance
White lightening	Mephedrone	Insect repellent	White dry powder
White lightening	MDPV	Natural stain remover	White dry powder
Zoom	MDPV	Bath salt	Beige powder
Energizing aromatherapy powder	MDPV and caffeine	Potpouri	Beige powder
Euphoria	Methylone and caffeine	Bath salt	Beige powder
Cotton cloud	Mephedrone, methylone, and MDPV	Bath salt	White crystalline powder
Cloud 9	Methylone and MDPV	Bath salt	Beige powder
Bayou ivory flower	Mephedrone	Bath salt	Beige powder
Cloud 10	MDPV	Not on product	Beige powder
White dove	Methylone	Bath salt	Beige powder
Dynamite	Methylone	Bath salt	White dry powder
Dynamite “plus”	MDPV	Bath salt	Beige powder
White china	MDPV and unknown compound	Bath salt	Beige powder
Snow day	Methylone and MDPV	Bath salt	Beige powder
Bolivian bath salts (scarface)	MDPV	Bath salt	White dry powder

Little is known of the mechanism of action of synthetic cathinones, but a clinical picture of a sympathomimetic syndrome has become evident. Methcathinone and methylone appear to inhibit membrane catecholamine transporters, suggesting a reuptake inhibition. Comparison of methcathinone and methylone to methamphetamine and methylenedioxyamphetamine (MDMA) showed similar effects on dopamine and norepinephrine reuptake inhibition, but methylone with its 3,4-methylenedioxy group showed increased serotonin reuptake inhibition.¹⁵ Animal studies with methylone showed potent monoamine release effects for dopamine and serotonin and less so for norepinephrine, and reflected reuptake inhibition of dopamine, norepinephrine, and serotonin.¹⁶ In a mouse model, MDPV increased dopamine concentrations but did not appear to affect serotonin concentrations.¹⁷ While the mechanism is not yet fully elucidated, it appears that the behavioral toxicity (including self-injurious behavior and schizophrenic-like psychoses) and movement disorders of synthetic cathinones may have a dopaminergic mechanism similar to amphetamines.^{22,23}

Within 8 months of their appearance on the US market, more than 1400 cases of misuse and abuse of "bath salts" had been reported to US poison centers in 47 of 50 states. On 6 January 2011, Louisiana passed an emergency rule placing six synthetic cathinones in Schedule I. The substances banned were 3,4-methylenedioxyamphetamine (methylone), 3,4-methylenedioxypropylamphetamine (MDPV), 4-methylmethcathinone (mephedrone), 4-methoxymethcathinone (methedrone), 3-fluoromethcathinone, and 4-fluoromethcathinone (fephedrone). The number of cases reported in Louisiana decreased dramatically after the ban was put in place on 6 January 2011 (Fig. 1). Within 3 months of this, 15 more states added synthetic cathinones to the controlled substances list as Schedule I drugs, either through temporary emergency rule or direct legislation (Kentucky, Alabama, Arkansas, Florida, Hawaii, Illinois, Idaho, Mississippi, North Dakota, Oregon, Utah, Virginia, Washington, Wisconsin, and Wyoming). Legislation is pending in a number of additional states. Timely information from poison centers on the bath salt outbreak was used by state and federal authorities during investigations to help track the extent of use and effects occurring from these new drugs. Close collaboration between state authorities and poison centers enhanced a rapid response, including legislation.

Conclusion

We report the emergence of a new group of substances of abuse in the USA, known as bath salts, with quantitative results of MDPV use in 19 patients. Calls to US poison centers as a result of the use and abuse of these drugs were first noted in 2010. Rapid analysis and identification of the synthetic cathinones involved in these substances as well as the coordinated response by two poison control centers have permitted a picture of this new epidemic to be presented. The growing number of cases together with the alarming severity of the effects caused by the abuse

of these substances prompted significant concern from both healthcare providers and legal authorities. Since the emergence of these bath salts, a growing number of states have designated six synthetic cathinones as Schedule I controlled substances. However, there are a large number of potential novel psychoactive "designer" drugs that may possibly be distributed in the future.²⁴ Changes to specific moieties may not be addressed in the current legislation, leaving clinical toxicologists, poison centers, and emergency physicians to face an on-going pattern of chasing the next ivory wave.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- Stephens A, Logina I, Liguts V, Aldins P, Eksteina I, Platkajis A, et al. A parkinsonian syndrome in methcathinone users and the role of manganese. *N Engl J Med* 2008; 358:1009–1017.
- de Bie RM, Gladstone RM, Strafella AP, Ko JH, Lang AE. Manganese-induced parkinsonian associated with methcathinone (ephedrine) abuse. *Arch Neurol* 2007; 64:886–889.
- Emerson TS, Cisek JE. Methcathinone: a Russian designer amphetamine infiltrates the rural Midwest. *Ann Emerg Med* 1993; 22:1897–1903.
- Lusthof KJ, Oosting R, Maes A, Verschraagen M, Dijkstra A, Sprong AGA. A case of extreme agitation and death after the use of mephedrone in the Netherlands. *Forensic Sci Intern* 2011; 206:e93–e95.
- Maskell PD, Paoli GD, Seneviratne C, Pounder DJ. Mephedrone (4-methylmethcathinone)-related deaths. *J Analyt Toxicol* 2011; 35:188–191.
- Regan L, Mitchelson M, Macdonald C. Mephedrone toxicity in a Scottish emergency department. *Emerg Med J* 2010 Dec 23. [Epub ahead of print] doi: 10.1136/emj.2010.103093.
- Durham M. Ivory Wave: the next mephedrone? *Emerg Med J* 2011 Mar 15. [Epub ahead of print] doi: 10.1136/emj.2011.112920.
- Wood DM, Davies S, Greene SL, Button J, Holt DW, Ramsey J, Dargan PI. Case series of individuals with analytically confirmed acute mephedrone toxicity. *Clin Toxicol* 2010; 40:924–927.
- Vardakou I, Pistos C, Spiliopoulou C. Drugs for youth via internet and the example of mephedrone. *Toxicol Lett* (2011) doi: 10.1016/j.toxlet.2010.12.014.
- Dargan PI, Albert S, Wood DW. Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. *QJ Med* 2010; 30 July [Epub ahead of print] doi: 10.1039/qjmed/hcq134.
- McElrath K, O'Neill C. Experiences with mephedrone pre- and post-legislative control: perceptions of safety and sources of supply. *Int J Drug Policy* 2011; 22:120–127.
- Brandt SD, Sumnall HR, Measham F, Cole J. Analyses of second generation "legal highs" in the UK: initial findings. *Drug Test Anal* 2010; 2:377–382.
- Karlia L, Reynaud M. GHB and synthetic cathinones: clinical effects and potential consequences. *Drug Test Anal* (2010) doi: 10.1002/dta.210.
- Bronstein AC, Spyker DA, Cantilena LR Jr., Green JL, Rumack BH, Giffin SL. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol* 2010; 48:979–1178.
- Cozzi NV, Sievert MK, Shulgin AT, Jacob III P, Ruoho AE. Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamine. *Eur J Pharmacol* 1999; 381:63–69.

16. Nagai F, Nonaka R, Satoh K, Kamimura H. The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. *Eur J Pharmacol* 2007; 559:132–137.
17. Fuma T, Kodama T, Honda Y, Tanaka T, Kubo Y, Ohashi N, et al. Influence of methylenedioxypropylvalerone on central nervous system using microdialysis method. *ChemBio Integrated Management* 2009; 5:62–72.
18. Durham M. Ivory wave: the next mephedrone? *Emerg Med J* 2011; doi 10.1136/emj.2011.112920.
19. Archer RP. Fluoromethcathinone, a new substance of abuse. *Forens Sci Int* 2009; 185:10–20.
20. Wood DM, Davies S, Puchnarewicz M, Button J, Archer R, Ovaska H, et al. Recreational use of mephedrone (4-methylenemethcathinone, 4-MMC) with associated sympatomimetic toxicity. *J Med Toxicol* 2010; 6:327–330.
21. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit* 2011; 33:257–263.
22. Kita T, Miyazaki I, Asanuma M, Takeshima M, Wagner GC. Dopamine-induced behavioral changes and oxidative stress in methamphetamine-induced neurotoxicity. *Int Rev Neurobiol* 2009; 88:43–64.
23. Greene SL, Kerr F, Braitberg G. Review article: amphetamines and related drugs of abuse. *Emerg Med Australas* 2008; 20:391–402.
24. Wohlfarth A, Weinmann W. Bioanalysis of new designer drugs. *Bioanalysis* 2010; 2:965–979.

68



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1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogs. A promising class of monoamine uptake inhibitors

Peter C. Meltzer^{†*}, David Butler[†], Jeffrey R. Deschamps^{††}, and Bertha K. Madras^{†††}

[†]*Organix Inc., 240 Salem Street, Woburn, MA 01801*

^{††}*Naval Research Laboratory, Washington, DC 20375*

^{†††}*Department of Psychiatry, Harvard Medical School and New England Regional, Primate Research Center, Southborough, MA 01772*

Abstract

Dopamine, serotonin and norepinephrine are essential for neurotransmission in the mammalian system. These three neurotransmitters have been the focus of considerable research since modulation of their production and their interaction at monoamine receptors has profound effects upon a multitude of pharmacological outcomes. Our interest has focused on neurotransmitter reuptake mechanisms in a search for medications for cocaine abuse. Herein we describe the synthesis and biological evaluation of an array of 2-aminopentanophenones. This array has yielded selective inhibitors of the dopamine and norepinephrine transporters with little effect upon serotonin trafficking. A subset of compounds had no significant affinity at 5HT_{1A}, 5HT_{1B}, 5HT_{1C}, D₁, D₂, or D₃ receptors. The lead compound, racemic 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4a**, was resolved into its enantiomers and the *S* isomer was found to be the most biologically active enantiomer. Among the most potent of these DAT/NET selective compounds are the 1-(3,4-dichlorophenyl)- (**4u**) and the 1-naphthyl- (**4t**) 2-pyrrolidin-1-yl-pentan-1-one analogs.

Introduction

The endogenous monoamines, dopamine, serotonin and norepinephrine are essential for neurotransmission in the mammalian system. These three neurotransmitters, their biological receptors, and their reuptake mechanisms are the focus of considerable research since modulation of their production and their interaction at monoamine receptors has profound effects upon a multitude of pharmacological outcomes.^{1–8} Dopamine, serotonin and norepinephrine are released into the synapse where their concentrations are regulated, at least in part, by reuptake proteins located in the presynaptic membrane.^{9,10} These reuptake mechanisms have been termed the dopamine transporter (DAT), serotonin transporter (SERT), and the norepinephrine transporter (NET). The DAT is the target of numerous therapeutic agents such as Ritalin® (methylphenidate), Adderall® (amphetamine), Wellbutrin® or Zyban® (bupropion). Our interest has focused on the DAT in a search for medications for cocaine abuse^{2,11–14} since cocaine's reinforcing and stimulant properties have long been associated with its propensity to bind to and inhibit monoamine transport systems, especially the DAT.^{15–24} Our work has concentrated on the design of compounds that inhibit all three monoamine uptake systems with different degrees of potency and selectivity. In the search for a new class of compounds that may provide a different access to agents that target the transport systems, our attention was drawn to bupropion (Figure 1), a compound marketed as an

*Corresponding author. Mail correspondence to: Dr. Peter Meltzer, Organix Inc., 240 Salem Street, Woburn, Massachusetts 01801 USA, Tel: 1-781-932-4142, Fax: 1-781-933-6695, E-mail: Meltzer@organixinc.com.

antidepressant (Wellbutrin®) as well as for smoking cessation (Zyban®). Bupropion is a 2-substituted aminopropiophenone,^{25,26} that has been explored extensively. Interestingly, and of relevance to the work which we describe later, the enantiomers of bupropion may not differ in their ability to inhibit biogenic amines.²⁷ Bupropion is structurally closely related to a 2-substituted aminopentanophenone, pyrovalerone (Figure 1).

In 1992 Lancelot reported that pyrovalerone inhibits the DAT and the NET, and is a weak inhibitor of the SERT.²⁸ Its synthesis was first reported by Heffe in 1964.²⁹ Stille³⁰ and Holliday³¹ confirmed its stimulant activity in animals and humans in 1963. In 1971 pyrovalerone was demonstrated to reduce symptoms of chronic fatigue in humans.³² Later studies in rat heart revealed that it inhibits NE uptake and effects the release of NE from storage or functional pools.^{25,33} In 1993 Vaugeois et al.³⁴ reported that pyrovalerone stimulated locomotor activity in mice (2mg/Kg) for up to 1 hour and that this duration of action paralleled the time course of its DAT occupancy. Notwithstanding this early clinical interest, the literature reveals little SAR on pyrovalerone. Lancelot et al.²⁸ reported the exchange of the phenyl ring for a thiophenyl ring. This exchange resulted in analogs of similar potency for both inhibition of DA and NE uptake. Further, an increase of size of the nitrogen containing ring from a 5-membered pyrrolidine to a 6-membered piperidine caused a substantial loss in binding potency at all uptake mechanisms. These researchers also reported that their analogs inhibited both DA and NE uptake but were less potent at inhibition at SERT, a finding very similar to that now reported for the analogs of the present study. Since then, one pharmacological study has appeared³⁴ in which pyrovalerone was shown to occupy striatal sites labeled with GBR12783, and to manifest an increase in locomotor activity. However, there are no further reports concerning SAR or biological enantioselectivity of pyrovalerone or analogs. Consequently, there is little directly relevant SAR to guide the selection of pyrovalerone analogs for evaluation as potential cocaine medication.

Herein we describe the synthesis and biological evaluation of a family of analogs of 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) **4a** and show, in general, that these compounds are potent inhibitors of the dopamine transporter (DAT) and norepinephrine transporter (NET), but are relatively poor inhibitors of the serotonin transporter (SERT). In addition, certain compounds were evaluated for affinity at 5HT_{1A}, 5HT_{1B}, 5HT_{1C}, D₁, D₂, and D₃ receptors and were found to be inactive.

Chemistry

The general route of synthesis of pyrovalerone and close analogs (Scheme 1) is straightforward and was first published by Heffe in 1964.²⁹ We have adopted this route wherever possible. The synthesis of target compounds **4** is presented in Scheme 1. Synthesis of **6**, **7**, **9f** and **9g** is shown in Scheme 2. Synthesis of compounds **9a–e** is presented in Scheme 3. The ketones (Scheme 1) **2d–f** are commercially available. Compound **2m** was prepared from **2k**. Ketones **2i–j** and **2n** were obtained from **2f** according to a literature procedure.³⁵ Other required ketones **2** were obtained either from aryl nitriles **1**, or by Friedel-Crafts acylation of suitably substituted aryl precursors.

Thus, aryl nitriles **1** were subjected to reaction with *n*-BuMgCl, followed by acidic hydrolysis to afford ketones **2h**, **2p**, **2r–u** and **2w** in excellent yields. Alternatively, ketones **2a**, **2g** and **2o** were prepared by Friedel-Crafts acylation of toluene, iodobenzene and acetanilide respectively with valeroyl chloride. These ketones **2** were then brominated selectively with bromine in the presence of a catalytic amount of aluminum trichloride to provide the α -bromoketones **3** quantitatively. Ring bromination did not occur under these conditions. The α -bromoketones were then used without further purification in the subsequent reactions with pyrrolidine at room temperature to provide **4a**, **d–j**, **m–p**, **r–u** and **4w**. Compounds **4k** and

4v were obtained by BBr_3 demethylation of **4m** and **4w** respectively. Sonogashira coupling of **4g** with propyne was used to prepare compound **4q**, and Stille coupling with the respective stannylated heterocycles was employed to prepare compounds **4x–z** from **4f**. Nitro compound **4l** was obtained by oxidation of compound **4o** with H_2O_2 /trifluoroacetic anhydride.

The resolution of racemic 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4a** was accomplished by recrystallization from CH_2Cl_2 /hexane of the diastereomeric salts obtained upon reaction with dibenzoyl-D-tartaric acid in refluxing ethanol (Scheme 4).

This provided the (2*R*)-pyrovalerone dibenzoyl-D-tartrate salt. The purity was determined by $^1\text{H-NMR}$ spectroscopy. The diastereomeric salt mixture showed two sets of triplets at $\delta = 0.73$ and 0.69 ppm (CDCl_3). These correspond to the ω -methyl protons of the pyrovalerone moieties of the (2*S*)-pyrovalerone dibenzoyl-D-tartrate and (2*R*)-pyrovalerone dibenzoyl-D-tartrate salts respectively. After four recrystallizations, the triplet at 0.73 ppm was no longer visible. The absence of the triplet attests to the diastereomeric purity of the compound, and this can be assumed to be >95% d.e. on the basis of the limits of sensitivity of the NMR experiment. It is noteworthy that the purified dibenzoyl-D-tartaric and L-tartaric acid diastereomeric salts of **4b** and **4c** are enantiomers and both resonate at $\delta 0.71$ for the ω -methyl. The assignment of the absolute optical configuration of this diastereomer was confirmed by X-ray structural analysis as (2*R*) (optical rotation was $[\alpha]_{\text{D}}^{20} = +59.6^\circ$ (c 1.06, EtOH)). Upon treatment with aqueous Na_2CO_3 and extraction into Et_2O , then treatment with HCl, this diastereomeric salt gave (2*R*)-pyrovalerone **4c**.

The (2*S*)-isomer **4b** was then obtained from the enriched mother liquors by reaction with dibenzoyl-L-tartaric acid, recrystallization of the diastereomeric salts (optical rotation was $[\alpha]_{\text{D}}^{20} = -61.1^\circ$ (c 1.07, EtOH)) and liberation of **4b** upon treatment with aqueous sodium carbonate. The chiral center does not epimerize under these conditions. The enantiomeric purity of **4b** and **4c** can be anticipated to be >95% ee, that is the same as the diastereomeric purity of the precursor dibenzoyl tartrate salts. Enantiomeric purity was confirmed by HPLC chiral resolution using a Chiralpak AD column. Each isomer was thus confirmed to be >99% pure (ee > 98%).

α,β -Unsaturated ketones **5a** and **5b** were obtained (Scheme 2) by dehydrobromination of **3a** and **3u** with $\text{Li}_2\text{CO}_3/\text{LiBr}$ in DMF. Reaction with pyrrolidine then gave **6a** and **6b** respectively. Compounds **7a** and **7b** were accessible *via* Mannich reaction of **3a** and **3b** with paraformaldehyde and pyrrolidine hydrochloride. Compound **3u** was also used to provide **9f** (reaction with butylamine) and **9g** (reaction with piperidine). Compounds **9a** and **b** were prepared (Scheme 3) by reaction of the appropriate α -bromoketones with pyrrolidine. Compounds **9c–e** were prepared from the 2-pyrrolidinyl **8**²⁹ by alkylation with propargyl bromide in the presence of sodium amide or by alkylation with allyl bromide followed by treatment with aqueous sodium hydroxide. Reduction of **4a** with LiAlH_4 gave **9h** and **9j** as a mixture of diastereomers, which were separated by flash column chromatography. All amines were converted to their HCl salts and recrystallized from EtOH/ Et_2O for biological assay with the exception of **4v** which was isolated as its HBr salt.

Biology

The ligand affinities (K_i , nM) for inhibition of the dopamine, serotonin and norepinephrine transporters were determined in competition studies with [^{125}I]RTI 55. Inhibition of monoamine uptake (IC_{50} , nM) was evaluated in competition with [^3H]dopamine, [^3H]serotonin, and [^3H]norepinephrine, and is presented in Table 1 and Table 2. In general, the analogs of 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one provide numerous examples of compounds that are potent inhibitors of the dopamine transporter and of dopamine reuptake. These compounds also inhibit NE reuptake with some potency, but are generally inactive at

the SERT and for serotonin reuptake inhibition. One notable exception to this selectivity is the naphthyl analog **4t**, which binds to all three transporters and inhibits reuptake at the nanomolar potency range. The lead compound, racemic pyrovalerone **4a**, has been demonstrated here to be biologically enantioselective since the DAT inhibitory potency of the racemic mixture of **4a** resides entirely with the 2*S*-enantiomer, **4b** (DAT K_i = 18.1 nM; DA IC_{50} = 16.3 nM). Of these DAT/NET compounds, the most potent is the 3,4-dichlorophenyl substituted **4u**, with DAT K_i = 11.5 nM and NET K_i = 37.8 nM. At this time it is unclear whether the inherent lipophilicity of both **4t** and **4u** is primarily responsible for their inhibitory potency. This question is currently being explored further.

Discussion

The lead compound for these studies was racemic 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) **4a** (Table 1). In our assays this compound proved a potent inhibitor of both RTI 55 binding (K_i = 21.4 nM, about 20-fold more potent than cocaine as measured in the same assay) and of dopamine (DA) uptake (IC_{50} = 52 nM, about 9-fold more potent than cocaine). Its potency of RTI 55 inhibition of the NET (K_i = 195 nM) as well as of norepinephrine (NE) uptake (IC_{50} = 28.3 nM) was also marked. It was found to be more potent than cocaine in this assay by about 11-fold and 13-fold respectively. The discrepancy between the inhibition of RTI 55 binding at the NET compared with inhibition of NE uptake was seen throughout this series of compounds. This discrepancy was first reported by Eshleman et al. in 1999.³⁶ They also noted that such differences were less evident in the case of the DAT and SERT. They suggested that this difference was likely a consequence of the ligand binding site on the NET being less closely linked to the sites of drug interactions with substrate and (NE) translocation than is the case for the DAT and the SERT.

Compound **4a** was relatively inert at the SERT, with potency in the micromolar range. Therefore racemic **4a** was potent at the DAT and NET, and selective against the SERT. Compound **4a** exists as two enantiomers; only racemic **4a** had been previously evaluated. The critical importance of absolute stereochemistry on biological function is well established. It is particularly relevant that both amphetamine (1-phenyl-2-aminopropane) and cathinone (1-phenyl-2-aminopropane-1-one) are biologically enantioselective with respect to their inhibition of DAT and NET.^{37,38} Indeed, the *S*-enantiomers are the eutomers in both cases. These two compounds bear strong structural similarities to the 1-aryl-2-pyrrolidin-1-yl-pentan-1-one analogs of this study, and therefore it was likely that their binding to, and thus inhibition of these transporters may likewise be similar. However, the structural similarity of the 1-aryl-2-pyrrolidin-1-yl-pentan-1-ones to the 2 β -carbomethoxy-3 α -aryl-8-azabicyclo [3.2.1]octane (tropane) class of DAT inhibitors is less clear. It is therefore interesting to note a comparison that utilized Dreiding models of WIN 35,428 (Figure 1) with enantiomers 2*S*-**4b** and 2*R*-**4c** (Scheme 4). The pyrrolidine nitrogens and the centroids of the aromatic rings were held coincident. In this rudimentary analysis the propyl side chain in the 2*S*-configuration overlapped with the C2- β -carbomethoxy of the tropane. However the 2*R*-configured compound had the propyl chain in a position similar to that of the 2 α -carbomethoxy of the tropane. It has been well established that the 2 α -carbomethoxy tropane analogs are less potent at the DAT than their 2 β -carbomethoxy counterparts. On this basis we had postulated that 2*S*-**4b** might be the active enantiomer at the DAT. As shown in Table I, enantiopure (2*R*-**4c**) is a poor inhibitor of RTI 55 binding at both DAT (K_i = 1,330 nM) and SERT (K_i > 10 μ M). In contrast, enantiopure (2*S*-**4b**) was quite potent at DAT (K_i = 18.1 nM) and selective (SERT: K_i > 2 μ M). It was interesting that this relative potency of the 2*S*-**4b** enantiomer extended to the NET. Here the 2*R*-**4c** enantiomer was effectively inert at NET inhibition and NE uptake and the potency of racemic **4a** resided exclusively in the 2*S*-**4b** enantiomer (NET: K_i = 109 nM; NE uptake: IC_{50} = 11.3 nM).

It is evident from the biological data (Table 1) that the inhibitory activities of these compounds cannot be easily correlated with varying electron density on the aromatic ring, nor with lipophilicity, or molecular refractivity. To this extent, this family of 1-aryl-2-pyrrolidin-1-yl-pentan-1-one analogs differs from other monoamine uptake inhibitors such as the 8-oxa-, 8-thia-, 8-aza- bicyclo[3.2.1]octanes,^{11,12,39,40} or methylphenidate analogs,^{41,42} where Structure Activity Relationships (SAR) were more easily discerned. Notwithstanding, certain relationships were evident among these analogs. Most clear was the fact that these 1-aryl-2-pyrrolidin-1-yl-pentan-1-one analogs were generally poor inhibitors of the SERT. Only two compounds (**4t**, **4u**) manifested SERT K_i s of <200 nM. The naphthyl analog **4t** inhibited SERT with modest potency ($K_i = 33.1$ nM) and the high lipophilicity of this compound (cLogP = 4.77) may be partially responsible for this potency. However, the lipophilic dichlorophenyl analog **4u** (cLog P = 5.01) manifested lesser SERT potency ($K_i = 199$ nM). Therefore lipophilicity was likely not the only factor that determined potency for **4t**. Within the family of analogs evaluated, the 3,4-dichlorophenyl analog **4u** was the most potent at DAT ($K_i = 11.5$ nM), followed by the 4-methylphenyl analog **4a**. At NET, only **4q** ($K_i = 69.8$ nM) and **4u** ($K_i = 37.8$ nM) were potent inhibitors of RTI 55 binding, although many compounds manifested substantial inhibition of NE uptake (**4a** $IC_{50} = 28.3$; **4b** $IC_{50} = 11.3$ nM; **4d** $IC_{50} = 56$ nM; **4f** $IC_{50} = 83$ nM; **4g** $IC_{50} = 46.5$ nM; **4h** $IC_{50} = 81$ nM; **4j** $IC_{50} = 12.4$ nM; **4k** $IC_{50} = 86.7$ nM; **4n** $IC_{50} = 22.8$ nM; **4q** $IC_{50} = 19.3$ nM; **4r** $IC_{50} = 19.7$ nM; **4s** $IC_{50} = 9.4$ nM; **4t** $IC_{50} = 11.7$ nM; **4u** $IC_{50} = 21$ nM; **4v** $IC_{50} = 7.6$ nM; **4x** $IC_{50} = 93$ nM; **9a** $IC_{50} = 18.5$ nM; **9b** $IC_{50} = 18.0$ nM; **9c** $IC_{50} = 88$ nM; **9d** $IC_{50} = 24.9$ nM).

It was particularly interesting that the catechol analog **4v** was one of the most potent inhibitors of NE uptake ($IC_{50} = 7.6$ nM) of those evaluated. Protection as the dimethoxy compound **4w** completely obliterated potency at all three monoamine transporters. The contrast between inhibition of the RTI 55 binding at the NET and inhibition of NE uptake is quite marked in the comparison of the disubstituted compounds **4u** (3,4-dichloro substitution) and **4v** (catechol moiety). In the former, the ratio of inhibition of NET binding to NE inhibition is about 2-fold, while in the latter this ratio is closer to 30-fold. The significance of this is unclear although this may again imply that the ligand binding site on the NET is only loosely associated with the site that effects NE translocation.³⁶

The position of the methyl substituent on the aromatic ring influenced NE uptake potency in an opposite sense to its influence on DAT inhibition, although DA uptake inhibition was similar. Thus, while the 3-methyl analog **4s** manifested an NE uptake $IC_{50} = 9.4$ nM, the 2-methyl **4r** and 4-methyl **4a** manifested IC_{50} s = 19.7, 28.3 nM respectively. A comparison of 4-methyl **4a** (DAT: $K_i = 21.4$ nM; NET: $K_i = 195$ nM), 2-methyl **4r** (DAT: $K_i = 59.7$ nM; NET: $K_i = 425$ nM), and 3-methyl **4s** (DAT: $K_i = 51$ nM; NET: $K_i = 216$ nM) 1-aryl-2-pyrrolidin-1-yl-pentan-1-ones showed that the 4-methyl **4a** was at least twice as potent as the 2-methyl **4r** and 3-methyl **4s** at DAT. The 3-methyl **4s** was about equipotent to the 4-methyl **4a** at the NET, although the 2-methyl **4r** remained about half as potent at the NET compared with **4a**. The most DAT vs. NET selective compound in this series was the 4-acetamido derivative **4o** with DAT $K_i = 30.2$ nM and NET $K_i = 4$ μ M.

The search for medications for cocaine abuse has centered, primarily, about two approaches. The first is the design of compounds that can act as cocaine substitutes and that manifest, in contrast to cocaine, slow onset rates and long durations of action.^{11,43-45} The second approach has been to seek cocaine antagonists.¹³ These compounds would manifest high potency for inhibition of cocaine binding to the DAT and little or no effect on DA uptake (i.e. DA trafficking). This has been the focus of numerous studies, and Deutsch and Scherri⁴⁶ have described the Discrimination Ratio (DR) as a guiding measure of potential cocaine antagonism. They defined the DR as the IC_{50} of DA uptake inhibition/ K_i for inhibition of DA uptake by the test compound. They pointed out that a DR < 10 is of little significance owing to differences

in conditions of each assay protocol. By this standard, none of the compounds here showed a $DR > 5$, and therefore none can be regarded as cocaine antagonists. Their use as potential medications for cocaine addiction may derive from onset and duration of action extensions, and these factors are currently under investigation.

Of note, the biaryl compounds **4x–z** lacked impressive potency at all sites; this, again, is contrary to the effects of such substitution in the bicyclo[3.2.1]octane series in both the 8-aza-⁴⁷ and 8-oxa series, as we shall report elsewhere.⁴⁸

Table 2 presents an array of compounds that explored the displacement of the pyrrolidine ring along the butyl chain (**6a, b**), the introduction of different C2 side chains (**9a, b**) as well as introduction of side chain unsaturation (**9c–e**), the effects of opening the pyrrolidine ring (**9f**), as well as expanding it to the 6-membered piperidine (**9g**). Finally, reduction of the ketone to obtain both isomers (**9h** and **9j**) is presented. The stereochemistry of these two diastereomers has not yet been determined. However, neither isomer shows any potency at DAT, SERT, and NET. A comparison of **6a** with **4a**, and **6b** with **4u** showed that essentially all inhibitory potency at all three transporters was lost when the pyrrolidine ring was moved one carbon along the chain. The nature of the pyrrolidine itself appears to be important since if it was opened (**9f**), or expanded (**9g**), the inhibitory potency was again much reduced compared with the parent compound **4u**. Lancelot et al.²⁸ had published a similar finding in their evaluation of 2-amino-1-(2-thienyl)-1-pentanones. Reduction of the ketone **4a** to yield the diastereomeric alcohols **9h** and **9j** provided totally inactive compounds. Modification of the alkyl chain of **4a** proved interesting. While a terminal acetylene (**9e**) resulted in a very substantial loss of potency at DAT, SERT, and NET, the allyl compounds **9c** and **9d** retained potency at DAT. The 3,4-dichloro compound **9d** (DAT: $K_i = 39.9$ nM) was again the more potent of the two, although NET potency declined substantially ($K_i = 509$ nM) compared with the comparative compound **4u** ($K_i = 37.8$ nM). Of these chain altered compounds, the isobutyl analog **9b** proved most interesting with a DAT $K_i = 13.7$ nM, but DA uptake $IC_{50} = 5.9$ nM. This compares with data for **4a** (DAT $K_i = 21.4$ and DA uptake $IC_{50} = 52$ nM). Thus the introduction of a branching methyl in the side chain has served to increase DA inhibition about 10-fold over the parent compound **4a**. The possible significance of this is not clear at this time.

The biological selectivity within this class of compounds proved striking. Thirteen compounds (**4b, f, k–m, o, p, r–t, y, 6a**, and **6b**) were evaluated for inhibition of $5HT_{1A}$, $5HT_{1B}$, $5HT_{1C}$, D_1 , D_2 , and D_3 receptors. The compounds were essentially inactive ($IC_{50} > 10$ μ M) in these assays. Two compounds (**4o**, which was a selective DAT inhibitor, and **4t**, which had similar potency at DAT and SERT) were selected for evaluation of locomotor activity. Both manifested a time and dose dependent stimulation of locomotor activity ($ED_{50} = 0.21$ mg/Kg and 2.2 mg/Kg respectively) with a duration of action of > 8 hours.

Conclusion

A family of 38 analogs of a lead compound 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) has been prepared. The biological activity at dopamine, serotonin and norepinephrine transporters has been determined. This family has yielded compounds that provide selective inhibitors of the dopamine and norepinephrine transporters with little effect upon serotonin trafficking. Furthermore, a subset of compounds selected for evaluation of their effect upon serotonin and dopamine receptors has shown them to be inactive at these sites. The lead compound **4a** has been demonstrated to be biologically enantioselective and it remains to be determined whether this enantioselectivity extends to other members of this family of compounds. Two compounds **4o** and **4t** manifested a time and dose dependent stimulation of locomotor activity with a duration of action of > 8 hours.

The inhibitory potency, the neurotransmitter selectivity profile and the inactivity at selected receptor sites of **4 k** and **4 o** have encouraged us to enter behavioral pharmacological evaluation in rat drug discrimination studies, and in vivo studies are currently ongoing.

Experimental Section

NMR spectra were recorded on a Jeol 300 NMR spectrometer (300.53 MHz for ^1H and 75.58 MHz for ^{13}C) with tetramethylsilane (TMS) as internal standard and DMSO- d_6 as solvent, with the exception of compounds **2** and **3**, which were measured in CDCl_3 . Optical rotations were measured on a Jasco P1010 polarimeter at room temperature. HPLC and MS data were obtained on an Agilent Series 1100 LC/MSD system. Melting points are uncorrected and were measured on a Mel-Temp melting point apparatus. Thin layer chromatography (TLC) was carried out on Baker Si 250F plates. Visualization was accomplished with iodine vapor, UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 μM (Silica gel). All reactions were conducted under an atmosphere of dry nitrogen. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Chemicals obtained from commercial sources were used as received. Room temperature is $22\text{ }^\circ\text{C} \pm 2\text{ }^\circ\text{C}$. Yields have not been optimized.

General Procedure A. Preparation of intermediate ketones, **2**

The ketones **2** were prepared (except where noted) by alkylation of the analogous commercially available nitrile compounds, followed by acidic hydrolysis. The nitrile (10 mmol) was added in several portions, over 0.5 h, to a solution of the *n*-BuMgCl (12 mmol) in toluene (20 mL). The reactions were monitored by TLC and heated where necessary. Generally, after 2 h stirring at room temperature, the reaction was complete. The reaction mixture was poured onto ice and concentrated H_2SO_4 (2 mL) was added. Hydrolysis of the intermediate imine usually occurred at room temperature after several minutes. However, for some substrates, heating was necessary to effect this transformation. The organics were extracted into Et_2O , dried (MgSO_4), filtered, and reduced *in vacuo* to an oil.

General Procedure B. Preparation of intermediate α -bromoketones, **3**

Compounds **3** were prepared by α -bromination of ketones **2**. The ketone (as a solution in Et_2O , or CH_2Cl_2 (for less soluble substrates)) was cooled in an ice bath and anhydrous AlCl_3 was added to the solution (1 – 5 mol%). Bromine (approximately 0.1 mol eq) was added to the solution all at once. Typically, after 10 min the solution changed from a light orange to colorless (if this change did not occur at $0\text{ }^\circ\text{C}$, then the mixture was warmed to room temperature). The remaining bromine (0.9 mol eq) was then added to the solution in a drop-wise manner over 5 min. The solution was neutralized (aqueous NaHCO_3), separated, dried (MgSO_4), filtered, and reduced to a lightly colored oil *in vacuo*. Yields were quantitative and the crude materials were sufficiently pure (^1H NMR) for use in the subsequent step.

General Procedure C. 1-Aryl-2-pyrrolidin-1-yl-pentan-1-ones (**4**)

Compounds **4** were prepared employing General Procedure C except where noted. α -Bromoketone **3** (10 mmol) was dissolved in Et_2O (10 mL) (EtOH is a suitable alternative solvent) and cooled on an ice bath. Pyrrolidine (22 mmol) was added all at once. The mixture became orange and an oil was observed to separate from the solution. After 1 – 24 h stirring at room temperature, the crude reaction mixture was partitioned between H_2O (10 mL) and Et_2O . The Et_2O layer was separated and the aqueous layer was washed with Et_2O ($2 \times 10\text{ mL}$). The ether layer was extracted with 1 M aqueous HCl ($2 \times 10\text{ mL}$), then backextracted into Et_2O ($3 \times 10\text{ mL}$) by basification to pH 8–9 with 20% aqueous Na_2CO_3 or 2 M aqueous NaOH. The Et_2O extracts were dried (MgSO_4) and filtered. The filtrate was treated with 2 M ethereal

HCl (usually 5 – 10 mL) until precipitation of solid or oil had ceased. Solids (oils were triturated to give solids) were collected by filtration and recrystallized from EtOH/Et₂O.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (**4a**)

1-(4-Methylphenyl)pentan-1-one **2a**, prepared by Friedel-Crafts acylation of toluene: ¹H NMR δ 7.86 (dd, 2H), 7.25 (dd, 2H), 2.92 (m, 2H), 2.41 (s, 3H), 1.71 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H) was brominated (General Procedure B) to provide 2-bromo-1-(4-methylphenyl)pentan-1-one **3a**: ¹H NMR δ 7.92 (d, 2H), 7.29 (d, 2H), 5.14 (dd, 1H), 2.43 (s, 3H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4a**, obtained as a colorless solid, was prepared from **3a** (General Procedure C). Yield 68%. Mp 180 °C (dec.); ¹H NMR δ 10.8 - 10.65 (br, 1H), 8.01 (d, 2H), 7.44 (d, 2H), 5.56 (m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, m, 1H), 3.35 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.42 (s, 3H), 2.15 - 1.85 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ¹³C NMR δ 196.1, 145.8, 132.1, 129.8, 129.0, 67.1, 53.5, 51.9, 31.8, 22.9, 21.3, 17.4, 13.7; APCI MS *m/z* 246 (M + 1); Anal. (C₁₆H₂₄ClNO.1/6H₂O) C, H, N, Cl.

(1*R*)-1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (**4c**) and (1*S*)-1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (**4b**)

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride, **4a**, (10.0 g, 35.5 mmol) was extracted into Et₂O from 20% aqueous Na₂CO₃ at pH 8–9. The ether was removed and the free base was dissolved in EtOH (50 mL) and heated to 70 °C. Dibenzoyl-*D*-tartaric acid (12.7 g, 35.5 mmol) in hot ethanol (150 mL) was added all at once to the pale yellow solution of free base. The resulting colorless solution was refluxed for 1 min, cooled, and the solvent was removed *in vacuo*. The residue was dissolved in CH₂Cl₂ (530 mL) and hexane (700 mL) was added with swirling. After 3 d, the resulting crystalline solid (9.1 g) was collected by filtration. ¹H NMR (CDCl₃) showed a diastereomeric excess (d.e.) of 70 – 75%. Three consecutive recrystallizations from CH₂Cl₂/hexane (300 mL/400 mL) gave a single diastereoisomer (6.1 g, 61%). Mp 100 – 120 °C; ¹H NMR δ 8.10 (d, 4H), 7.87 (d, 2H), 7.51 (t, 2H), 7.37 (t, 4H), 7.18 (d, 2H), 5.91 (s, 2H), 5.37 (t, 1H), 3.75 (br, m, 2H), 2.32 (s, 3H), 2.0 - 1.8 (br, m, 6H), 1.4 - 1.1 (br, m, 4H), 0.71 (t, 3H). X-ray structural analysis of this compound showed it to be the dibenzoyl-*D*-tartaric acid salt of (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one. [α]_D²⁰ = +59.6° (c 1.06, EtOH).

The salt was dissolved in 20% aqueous Na₂CO₃ and extracted into Et₂O. The Et₂O layer was collected, dried and filtered. Ethereal 2M HCl was added to this solution to provide a white solid that was recrystallized from EtOH/Et₂O to give pure (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride, **4c**. The physical properties of this compound were identical with those of the racemic material **4a**.

The residues from recrystallization of the dibenzoyl-*D*-tartaric acid (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one, were combined and the free base was liberated with 20% aqueous Na₂CO₃. The ethereal extracts were washed once with 20% aqueous Na₂CO₃, dried (MgSO₄), filtered, and reduced *in vacuo* to an oil (5.2 g, 21 mmol). This oil was dissolved in hot EtOH (50 mL), and a solution of dibenzoyl-*L*-tartaric acid (7.5 g, 21 mmol) in hot EtOH (100 mL) was added with swirling. The mixture was refluxed for 1 min, cooled, and the solvent was removed *in vacuo*. Four recrystallizations, as described above, gave a single diastereoisomer (5.4 g, 50%). X-ray structural analysis confirmed the diastereomeric salt of dibenzoyl-*L*-tartaric acid (1*S*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one. [α]_D²⁰ = -61.1° (c 1.07, EtOH).

The hydrochloride salt of (1*S*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one, **4b** was then prepared as described above for (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one.

The enantiomeric purities of **4b** and **4c** were confirmed by chiral HPLC (Chiralpak AD, 0.46 × 25cm; Flow rate 1 mL/min; eluent 2–10% EtOH/hexanes + 0.1 % NEt₃). **4b**: t_R = 6.77 min, purity 99.8%; **4c**: t_R = 5.85 min, purity 100%.

Single-crystal X-ray analysis of dibenzoyl-D-tartaric acid salt of (1R)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one

Monoclinic crystals of the purified title compound were obtained from CH₂Cl₂/hexane. A representative crystal was selected and a 1.54178 Å data set was collected at 198 °K. Pertinent crystal, data collection and refinement parameters: crystal size, 0.32 × 0.12 × 0.03 mm; cell dimensions, *a* = 7.8458 (10) Å, *b* = 13.4366 (2) Å, *c* = 18.2054 (3) Å, α = 90°, β = 93.717 (10)°, γ = 90°; formula, C₄₀H₅₁NO₉; formula weight = 689.82; volume = 1915.19 (5) Å³; calculated density = 1.196 g cm⁻³; space group = P2₁; number of reflections = 11525 of which 5630 were considered independent (R_{int} = 0.0244). Refinement method was full-matrix least-squares on F₂. The final *R*-indices were [*I* > 2σ (*I*)] R1 = 0.0520, wR2 = 0.1439.

Single-crystal X-ray analysis of dibenzoyl-L-tartaric acid (1S)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one

Monoclinic crystals of the purified dibenzoyl-L-tartaric acid (1S)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one were obtained from CH₂Cl₂/hexane. A representative crystal was selected and a 1.54178 Å data set was collected at 153 °K. Pertinent crystal, data collection and refinement parameters: crystal size, 0.58 × 0.16 × 0.05 mm; cell dimensions, *a* = 7.8456 (1) Å, *b* = 13.4605 (2) Å, *c* = 18.2956 (3) Å, α = 90°, β = 93.5910 (10)°, γ = 90°; formula, C₄₀H₅₁NO₉; formula weight = 689.82; volume = 1930.88 (5) Å³; calculated density = 1.186 g cm⁻³; space group = P2₁; number of reflections = 9774 of which 5860 were considered independent (R_{int} = 0.0317). Refinement method was full-matrix least-squares on F₂. The final *R*-indices were [*I* > 2σ (*I*)] R1 = 0.0537, wR2 = 0.1410.

2-Pyrrolidin-1-yl-1-phenylpentan-1-one (4d)

Commercially available **2d** was brominated (General Procedure B) to give 2-bromo-1-phenylpentan-1-one **3d**: ¹H NMR δ 8.02 (d, 2H), 7.62 (m, 1H), 7.49 (t, 2H), 5.15 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.4 (m, 2H), 0.99 (t, 3H). Compound **4d**, obtained as a colorless solid, was prepared from **3d** (General Procedure C) (51% yield); Mp 173 °C; ¹H NMR δ 10.9 - 10.6 (br, 1H), 8.11 (d, 2H), 7.78 (t, 1H), 7.64 (t, 2H), 5.62 (m, 1H), 3.64 (br, m, 1H), 3.49 (br, m, 1H), 3.26 (br, m, 1H), 3.10 (br, m, 1H), 2.15 - 1.85 (m, 6H), 1.4 - 1.2 (m, 1H), 1.2 - 0.95 (m, 1H), 0.78 (t, 3H); ¹³C NMR 196.7, 134.9, 134.5, 129.2, 128.8, 67.3, 53.6, 51.9, 31.7, 22.9, 17.4, 13.7; APCI MS *m/z* 232 (M + 1); Anal. (C₁₅H₂₂ClNO) C, H, N, Cl.

1-(4-Fluorophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4e)

Commercially available **2e** was brominated (General Procedure B) to give 2-bromo-1-(4-fluorophenyl)pentan-1-one **3e**: ¹H NMR δ 8.05 (dd, 2H), 7.16 (dd, 2H), 5.09 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4e**, obtained as a colorless solid, was prepared from **3e** (General Procedure C) (84% yield). Mp 218 °C (dec.); ¹H NMR δ 10.7 - 10.5 (br, 1H), 8.19 (m, 2H), 7.49 (t, 2H), 5.6 - 5.5 (br, m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, 1H), 2.15 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.79 (t, 3H); ¹³C NMR δ 195.2, 132.2, 132.0, 131.3, 116.6, 116.3, 67.2, 53.5, 51.9, 31.7, 22.9, 17.4, 13.7; APCI MS *m/z* 250 (M + 1); Anal. (C₁₅H₂₁ClFNO) C, H, N, Cl.

1-(4-Bromophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4f)

Commercially available **2f** was brominated (General Procedure B) to give 2-bromo-1-(4-bromophenyl)pentan-1-one **3f**: ¹H NMR δ 7.88 (d, 2H), 7.63 (d, 2H), 5.06 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4f**, obtained as a colorless solid, was

prepared from **3f** (General Procedure C) (62% yield). Mp 200 °C (dec.); ¹H NMR δ 10.7 - 10.5 (br, 1H), 8.03 (d, 2H), 7.87 (d, 2H), 5.56 (m, 1H), 3.7 - 3.55 (br, m, 1H), 3.55 - 3.4 (br, m, 1H), 3.35 - 3.1 (br, m, 1H), 3.1 - 3.0 (br, m, 1H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ¹³C NMR δ 196.0, 133.4, 132.4, 130.8, 129.4, 67.4, 53.7, 51.9, 31.6, 22.9, 17.3, 13.7; APCI MS *m/z* 312, 310 (M + 1); Anal. (C₁₅H₂₁BrClNO) C, H, N, Cl.

1-(4-Iodophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4g)

1-(4-Iodophenyl)pentan-1-one **2g**, prepared by Friedel-Crafts acylation of 4-iodobenzene and purified by distillation (Bp 112 °C, 0.1 mm Hg) and recrystallization from EtOH: (11% yield); ¹H NMR δ 7.82 (d, 2H), 7.67 (d, 2H), 2.92 (t, 2H), 1.71 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H) was brominated (General Procedure B) to give 2-bromo-1-(4-iodophenyl)pentan-1-one **3g**: ¹H NMR δ 7.85 (d, 2H), 7.72 (d, 2H), 5.06 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4g** was prepared from **3g** (General Procedure C) (37% yield); Mp 218 °C (dec.); ¹H NMR δ 10.75 - 10.65 (br, 1H), 8.05 (d, 2H), 7.84 (d, 2H), 5.53 (m, 1H), 3.7 - 3.65 (br, 1H), 3.65 - 3.5 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ¹³C NMR δ 196.3, 138.2, 133.6, 130.3, 104.6, 67.3, 53.7, 51.9, 31.6, 22.9, 17.3, 13.7; APCI MS *m/z* 358 (M + 1); Anal. (C₁₅H₂₁ClINO) C, H, N, Cl.

1-(3-Iodophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4h)

1-(3-Iodophenyl)pentan-1-one **2h**, prepared in 29 % yield from 3-iodobenzonitrile (General Procedure A) and purified by column chromatography (3% EtOAc/hexane): *R_f* 0.25 (5% EtOAc/hexane); ¹H NMR δ 8.28 (t, 1H), 7.90 (m, 2H), 7.21 (t, 1H), 2.93 (t, 2H), 1.71 (m, 2H), 1.40 (m, 2H), 0.96 (t, 3H); ¹³C NMR δ 199.1, 141.6, 138.8, 137.0, 130.3, 127.1, 94.4, 38.3, 26.2, 22.4, 13.9, was brominated (General Procedure B) to provide 2-bromo-1-(3-iodophenyl)pentan-1-one **3h**: ¹H NMR δ 8.33 (dd, 1H), 7.96 (ddd, 1H), 7.93 (ddd, 1H), 7.22 (d, 1H), 5.05 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4h**, obtained as a colorless solid, was prepared from **3h** (General Procedure C) (20% yield); Mp 203 °C (dec.); ¹H NMR δ 10.6 - 10.4 (br, 1H), 8.39 (s, 1H), 8.14 (d, 1H), 8.07 (d, 1H), 7.44 (t, 1H), 5.51 (m, 1H), 3.7 - 3.55 (br, m, 1H), 3.55 - 3.4 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.1 - 0.9 (m, 1H), 0.79 (t, 3H); ¹³C NMR δ 195.7, 143.3, 136.9, 136.1, 131.8, 131.3, 128.0, 95.7, 67.5, 53.8, 51.9, 31.5, 22.8, 17.2, 13.6; APCI MS *m/z* 358 (M + 1); Anal. (C₁₅H₂₁ClINO) C, H, N, Cl.

4-(2-Pyrrolidin-1-yl-pentanoyl)benzoyl nitrile hydrochloride (4i)

4-(2-Bromopentanoyl)benzoyl nitrile, **3i**: ¹H NMR δ 8.11 (d, 2H), 7.80 (d, 2H), 5.07 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 1.00 (t, 3H) was prepared (General Procedure B) from 4-cyanovalerophenone **2i**³⁵ and converted to **4i** as described in General Procedure C (70% yield); Mp 197 - 199 °C (dec.); ¹H NMR δ 10.9 - 10.7 (br, 1H), 8.24 (d, 2H), 8.14 (d, 2H), 5.7 - 5.55 (br, m, 1H), 3.7 - 3.6 (br, m, 1H), 3.6 - 3.5 (br, m, 1H), 3.3 - 3.1 (br, m, 2H), 2.1 - 1.8 (m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.77 (t, 3H); ¹³C NMR δ 196.2, 137.5, 133.2, 129.4, 117.9, 116.6, 67.8, 53.7, 51.9, 31.3, 22.9, 17.2, 13.7; APCI MS *m/z* 257 (M + 1); Anal. (C₁₆H₂₁ClN₂O.1/4H₂O) C, H, N, Cl.

1-(4-Hydroxymethylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4j)

2-Bromo-1-(4-hydroxymethylphenyl)-pentan-1-one **3j**: ¹H NMR δ 8.01 (d, 2H), 7.48 (d, 2H), 5.15 (dd, 1H), 4.79 (br, d, 2H), 2.25 - 2.05 (m, 2H), 2.05 - 1.95 (br, 1H), 1.65 - 1.4 (m, 2H), 0.99 (t, 3H) was prepared (General Procedure B) from 1-(4-hydroxymethylphenyl)pentan-1-one **2j**³⁵ and converted to **4j** as described in General Procedure C (79% yield); Mp 186 - 187 °C (dec.); ¹H NMR δ 10.6 - 10.4 (br, 1H), 8.05 (d, 2H), 7.56 (d, 2H), 5.7 - 5.4 (br, m, 2H), 4.62 (s, 2H), 3.7 - 3.55 (m, 1H), 3.55 - 3.3 (m, 1H), 3.35 - 3.15 (m, 1H), 3.1 - 3.0 (m, 1H), 2.1 - 1.8

(m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.2, 150.4, 132.8, 128.8, 126.7, 67.4, 62.2, 53.8, 51.9, 31.8, 22.8, 17.3, 13.7; APCI MS m/z 262 (M + 1); Anal. ($\text{C}_{16}\text{H}_{24}\text{ClNO}_2 \cdot 1/4\text{H}_2\text{O}$) C, H, N, Cl.

1-(4-Hydroxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4k)

1-(4-Methoxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4m** (9.00 g, 30.3 mmol) was freed from its hydrochloride salt by basification to pH 8–9 with 20% aqueous Na_2CO_3 and extraction into CH_2Cl_2 . The free base was dissolved in CH_2Cl_2 (50 mL) and cooled to -78°C . BBr_3 (90 mL, 1.0 M solution in CH_2Cl_2 , 90 mmol) was added to the solution over 0.5 h. The mixture was stirred for a further 1 h before warming gradually to room temperature. The gummy mixture, which became difficult to stir, was quenched after 2 h with saturated aqueous NaHCO_3 and the neutral organics were extracted into CH_2Cl_2 . A white solid precipitated from the aqueous layer and was collected on a frit (2.8 g). This material was dissolved in Et_2O and treated with 2 M ethereal HCl. The solid obtained was collected by filtration then recrystallized from ethanol to give pure 1-(4-hydroxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one as its hydrochloride **4k** (2.9 g, 34%). Mp 235°C (dec.); ^1H NMR (CD_3OD) δ 7.99 (d, 2H), 6.93 (d, 2H), 5.26 (t, $J = 5.5$ Hz, 1H), 3.7 - 3.0 (br, 4H), 2.2 - 1.9 (br, m, 6H), 1.4 - 1.1 (m, 2H), 0.89 (t, 3H); ^{13}C NMR δ 195.0, 156.8, 132.9, 127.3, 117.0, 69.8, 33.9, 24.1, 18.6, 14.2; APCI MS m/z 248 (M + 1); Anal. ($\text{C}_{15}\text{H}_{22}\text{ClNO}_2$) C, H, N, Cl.

1-(4-Nitrophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4l)

A 50% w/w aqueous solution of H_2O_2 (7 mL, 0.12 mol) was added to CH_2Cl_2 (50 mL) which had been cooled on an ice bath. Trifluoroacetic anhydride (23 mL, 0.14 mol) was added slowly *via* syringe. The solution was then warmed to room temperature. *N*-[4-(2-Pyrrolidin-1-ylpentanoyl)phenyl]acetamide hydrochloride **4o** (4.5 g, 18 mmol) was added over 20 min, and the mixture was heated to reflux for 1 h. The solution was cooled, then quenched cautiously with aqueous Na_2SO_3 (100 mL of a 1.6 M solution, 0.16 mol). The organics were separated and extracted into Et_2O , then back-extracted into 1 M aqueous HCl. The acidic extracts were basified with 20% aqueous Na_2CO_3 to pH 8–9 and extracted into Et_2O . The organic extracts were dried (MgSO_4), filtered, and then treated with 2 M ethereal HCl. The resulting white precipitate was collected on a frit, dissolved in water, and then freeze-dried to give pure 1-(4-nitrophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride **4l** (290 mg, 5%). Mp 189°C (dec.); ^1H NMR δ 10.8 - 10.6 (br, 1H), 8.45 (d, 2H), 8.32 (d, 2H), 5.65 (m, 1H), 3.7 - 3.3 (br, m, 2H), 3.3 - 3.1 (br, m, 2H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.0, 150.8, 138.7, 130.4, 124.3, 68.1, 53.9, 52.0, 31.2, 22.9, 17.2, 13.7; APCI MS m/z 277 (M + 1); Anal. ($\text{C}_{15}\text{H}_{21}\text{ClN}_2\text{O}_3 \cdot 1/2\text{H}_2\text{O} \cdot 1/10\text{HCl}$) C, H, N, Cl.

1-(4-Methoxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4m)

1-(4-Methoxyphenyl)pentan-1-one **2m**, obtained by methylation of commercially available 1-(4-hydroxyphenyl)pentan-1-one, **2k**, with $\text{MeI}/\text{K}_2\text{CO}_3$ in refluxing acetone, was brominated (General Procedure B) to afford 2-bromo-1-(4-methoxyphenyl)pentan-1-one **3m**: ^1H NMR δ 8.01 (d, 2H), 6.96 (d, 2H), 5.12 (dd, 1H), 3.89 (s, 3H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4m** was obtained as a colorless solid from **3m** (General Procedure C) (68% yield); ^1H NMR δ 10.8 - 10.6 (br, 1H), 8.10 (d, 2H), 7.15 (d, 2H), 5.55 (m, 1H), 3.89 (s, 3H), 3.7 - 3.55 (br, m, 1H), 3.55 - 3.4 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.1 - 2.95 (br, m, 1H), 2.15 - 1.85 (br, m, 6H), 1.34 - 1.15 (m, 1H), 1.15 - 1.0 (m, 1H), 0.79 (t, 3H); ^{13}C NMR δ 194.7, 164.5, 131.4, 127.4, 114.5, 66.7, 55.8, 53.4, 51.8, 32.0, 22.9, 17.5, 13.7; APCI MS m/z 262 (M + 1); Anal. ($\text{C}_{16}\text{H}_{24}\text{ClNO}_2 \cdot 1/2\text{H}_2\text{O} \cdot 1/2\text{HCl}$) C, H, N, Cl.

4-(2-Pyrrolidin-1-yl-pentanoyl)benzoic acid methyl ester hydrochloride (4n)

4-(2-Bromopentanoyl)benzoic acid methyl ester **3n**: $^1\text{H NMR } \delta$ 8.14 (d, 2H), 8.06 (d, 2H), 5.13 (t, 1H), 3.96 (s, 3H), 2.2 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 1.00 (t, 3H) was prepared (General Procedure B) from **2n**³⁵ and converted to **4n** as described in General Procedure C (77% yield); Mp 202 °C (dec.); $^1\text{H NMR } \delta$ 10.7 - 10.5 (br, 1H), 8.3 - 8.1 (m, 4H), 5.58 (m, 1H), 3.91 (s, 3H), 3.7 - 3.5 (br, m, 2H), 3.3 - 3.05 (br, m, 2H), 2.15 - 2.85 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.77 (t, 3H); $^{13}\text{C NMR } \delta$ 196.5, 165.3, 137.6, 134.6, 129.8, 129.2, 67.9, 53.9, 52.7, 51.9, 31.4, 22.9, 17.2, 13.7; APCI MS m/z : 290 ((M + 1), 100%), 275; Anal. ($\text{C}_{17}\text{H}_{24}\text{ClNO}_3$) C, H, N, Cl.

N-[4-(2-Pyrrolidin-1-yl-pentanoyl)phenyl]acetamide hydrochloride (4o)

N-(4-Pentanoylphenyl)acetamide, **2o**, prepared in 60% yield by Friedel-Crafts acylation of acetanilide in CS_2 , and purified by recrystallization from hot MeOH: $^1\text{H NMR } \delta$ 7.94 (d, 2H), 7.61 (d, 2H), 7.41 (br, s, 1H), 2.94 (t, 2H), 2.22 (s, 3H), 1.8 - 1.65 (m, 2H), 1.45 - 1.35 (m, 2H), 0.95 (t, 3H); $^{13}\text{C NMR } \delta$ 168.4, 142.0, 132.9, 129.5, 118.8, 38.2, 26.6, 24.8, 22.5, 14.0, was brominated (General Procedure B) to provide *N*-[4-(2-bromopentanoyl)phenyl]acetamide, **3o**: $^1\text{H NMR } \delta$ 8.00 (d, 2H), 7.65 (br, m, 3H), 5.12 (dd, 1H), 2.23 (s, 3H), 2.2 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4o** was prepared from **3o** as described in General Procedure C (56% yield); Mp 195 °C (dec.); $^1\text{H NMR } \delta$ 10.76 (s, 1H), 10.55 - 10.35 (br, 1H), 8.05 (d, 2H), 7.85 (d, 2H), 5.5 - 5.4 (br, m, 1H), 3.7 - 3.55 (br, 1H), 3.5 - 3.3 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.13 (s, 3H), 2.1 - 1.8 (br, m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 1.0 (m, 1H), 0.79 (t, 3H); $^{13}\text{C NMR } \delta$ 194.8, 169.4, 145.4, 130.4, 128.8, 118.4, 67.0, 53.6, 51.9, 32.0, 24.2, 22.8, 17.4, 13.7; APCI MS m/z 289 (M + 1); Anal. ($\text{C}_{17}\text{H}_{25}\text{ClN}_2\text{O}_2 \cdot 1/2\text{H}_2\text{O}$) C, H, N, Cl.

2-Pyrrolidin-1-yl-1-(4-trifluoromethylphenyl)pentan-1-one hydrochloride (4p)

1-(4-Trifluoromethylphenyl)pentan-1-one **2p**, prepared in 95% yield from 4-trifluoromethylbenzotrile (General Procedure A): $^1\text{H NMR } \delta$ 8.06 (d, 2H), 7.43 (d, 2H), 3.00 (t, 2H), 1.74 (m, 2H), 1.41 (m, 2H), 0.96 (t, 3H) was brominated (General Procedure B) to provide 2-bromo-1-(4-trifluoromethylphenyl)pentan-1-one, **3p**: $^1\text{H NMR } \delta$ 8.13 (d, 2H), 7.76 (d, 2H), 5.11 (dd, 1H), 2.25 - 2.1 (m, 2H), 1.7 - 1.4 (m, 2H), 1.00 (t, 3H). Compound **4p** was prepared from **3p** as described in General Procedure C (44% yield); Mp 228 °C (dec.); $^1\text{H NMR } \delta$ 10.8 - 10.6 (br, 1H), 8.28 (d, 2H), 8.03 (d, 2H), 5.62 (m, 1H), 3.7 - 3.4 (br, m, 2H), 3.3 - 3.05 (br, m, 2H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.78 (t, 3H); $^{13}\text{C NMR } \delta$ 196.2, 137.4, 129.7, 126.3, 67.8, 53.8, 51.9, 31.3, 22.9, 17.2, 13.7; APCI MS m/z 300 (M + 1); Anal. ($\text{C}_{16}\text{H}_{21}\text{ClF}_3\text{NO}$) C, H, N, Cl.

1-(4-Propynylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4q)

1-(4-Iodophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (500 mg, 1.27 mmol) **4g**, was taken up in Et_2NH (10 mL) and degassed by purging with N_2 . $[\text{PdCl}_2(\text{PPh}_3)_2]$ (18 mg, 2.5×10^{-5} mol) and CuI (2.4 mg, 1.3×10^{-5} mol) were added to the stirring solution at room temperature. Propyne was then bubbled through the resulting yellow mixture for 7 h. The mixture was filtered and reduced to an oil *in vacuo*. The oil was taken up in Et_2O and extracted into 1M aqueous HCl, then back-extracted into Et_2O by treatment with 20% aqueous Na_2CO_3 until pH 8-9. The organic extracts were dried (MgSO_4), filtered, and reduced *in vacuo* to a pale yellow oil. The hydrochloride was prepared from 2M ethereal HCl and recrystallized twice from $\text{EtOH}/\text{Et}_2\text{O}$ to give pure 1-(4-propynylphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4q** as a colorless crystalline solid (260 mg, 67%). Mp 231 °C (dec.); $^1\text{H NMR } \delta$ 10.6 - 10.4 (br, 1H), 8.04 (d, 2H), 7.62 (d, 2H), 5.55 - 5.4 (br, m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.3 - 3.1 (br, m, 1H), 3.1 - 2.95 (br, m, 1H), 2.12 (s, 3H), 2.1 - 1.8 (br, m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); $^{13}\text{C NMR } \delta$ 195.9, 133.1, 131.9,

129.9, 129.1, 92.1, 79.0, 67.5, 53.8, 51.9, 31.7, 22.8, 17.2, 13.7, 4.1; APCI MS m/z 270 ($M + 1$); Anal. ($C_{18}H_{24}ClNO$) C, H, N, Cl.

1-(2-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4r)

1-(2-Methylphenyl)pentan-1-one **2r** obtained in 75% yield from 2-methylbenzotrile (General Procedure A) and purified by distillation (Bp 58 – 60°C, 0.05 mm Hg): 1H NMR δ 7.62 (m, 1H), 7.36 (m, 1H), 7.26 (m, 2H), 2.89 (t, 2H), 2.48 (s, 3H), 1.68 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H) was brominated (General Procedure B) to afford 2-bromo-1-(2-tolyl)pentan-1-one **3r**: 1H NMR δ 7.63 (d, 1H), 7.42 (m, 1H), 7.27 (m, 2H), 5.05 (dd, 1H), 2.50 (s, 3H), 2.25 - 2.0 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4r** was prepared from **3r** as described in General Procedure C (39% yield); 1H NMR δ 10.9 - 10.7 (br, 1H), 8.12 (d, 1H), 7.58 (t, 1H), 7.44 (t, 2H), 5.56 (m, 1H), 3.7 - 3.5 (br, 2H), 3.35 - 3.1 (br, m, 2H), 2.46 (s, 3H), 2.1 - 1.7 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.76 (t, 3H); ^{13}C NMR δ 199.1, 138.8, 134.4, 133.2, 132.3, 130.0, 126.2, 68.9, 53.5, 51.8, 31.4, 23.0, 20.7, 17.5, 13.7; APCI MS m/z 246 ($M + 1$); Anal. ($C_{16}H_{24}ClNO \cdot H_2O$) C, H, N, Cl.

1-(3-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4s)

1-(3-Methylphenyl)pentan-1-one **2s**, obtained in 98% yield from 3-methylbenzotrile (General Procedure A) and purified by distillation (Bp 64 – 68°C, 0.1 mm Hg): 1H NMR δ 7.86 (d, 2H), 7.26 (d, 2H), 2.94 (t, 2H), 2.41 (s, 3H), 1.71 (m, 2H), 1.41 (m, 2H), 0.95 (t, 3H), was brominated (General Procedure B) to provide 2-bromo-1-(3-methylphenyl)pentan-1-one, **3s**: 1H NMR δ 7.81 (m, 2H), 7.40 (m, 2H), 5.15 (dd, 1H), 2.43 (s, 3H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4s** was prepared from **3s** as described in General Procedure C (53% yield); Mp 166 °C (dec.); 1H NMR δ 10.8 - 10.6 (br, 1H), 7.90 (d, 2H), 7.65 - 7.5 (m, 2H), 5.57 (m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.42 (s, 3H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.7, 138.8, 135.6, 134.5, 129.1, 126.1, 67.4, 53.6, 51.9, 31.7, 22.9, 20.8, 17.3, 13.7; APCI MS m/z 246 ($M + 1$); Anal. ($C_{16}H_{24}ClNO$) C, H, N, Cl.

1-Naphthalen-2-yl-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4t)

1-Naphthalen-2-yl-pentan-1-one **2t** prepared in 95 % yield from naphthalene-2-carbonitrile (General Procedure A): 1H NMR δ 8.48 (s, 1H), 8.04 (dd, 1H), 7.97 (d, 1H), 7.90 (m, 2H), 7.57 (m, 2H), 3.11 (t, 2H), 1.79 (m, 2H), 1.44 (m, 2H), 0.98 (t, 3H) was brominated (General Procedure B) to afford 2-bromo-1-naphthalen-2-yl-pentan-1-one **3t**: 1H NMR δ 8.55 (s, 1H), 8.1 - 7.85 (m, 4H), 7.60 (m, 2H), 5.33 (dd, 1H), 2.3 - 2.1 (m, 2H), 1.7 - 1.4 (m, 2H), 1.01 (t, 3H). Compound **4t** was prepared from **3t** as described in General Procedure C (51% yield); Mp 221 – 223 °C (dec.); 1H NMR δ 10.8 - 10.6 (br, 1H), 8.92 (s, 1H), 8.2 - 8.0 (m, 4H), 7.75 (dt, 2H), 5.73 (m, 1H), 3.75 - 3.6 (br, 1H), 3.6 - 3.4 (br, m, 1H), 3.35 - 3.1 (br, m, 2H), 2.2 - 1.8 (m, 6H), 1.4 - 1.2 (m, 1H), 1.2 - 1.0 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.6, 135.7, 132.0, 131.8, 131.7, 129.9, 129.7, 129.0, 127.8, 127.5, 123.4, 67.3, 53.6, 52.0, 31.9, 22.9, 17.4, 13.7; APCI MS m/z 282 ($M + 1$); Anal. ($C_{19}H_{24}ClNO$) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4u)

1-(3,4-Dichlorophenyl)pentan-1-one **2u** prepared in 93% yield from 3,4-dichlorobenzotrile (General Procedure A) and used crude in the next step of the reaction: 1H NMR δ 8.03 (d, 1H), 7.78 (dd, 1H), 7.54 (d, 1H), 2.92 (t, 2H), 1.71 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H) was brominated (General Procedure B) to afford 2-bromo-1-(3,4-dichlorophenyl)pentan-1-one **3u**: 1H NMR δ 8.09 (d, 1H), 7.84 (dd, 1H), 7.55 (d, 1H), 5.02 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4u** was prepared from **3u** as described in General Procedure C (32% yield); Mp 195 °C (dec.); 1H NMR δ 10.8 - 10.6 (br, 1H), 8.35 (d, 1H), 8.04 (dd, 1H), 7.94 (d, 1H), 5.58 (m, 1H), 3.7 - 3.6 (br, 1H), 3.6 - 3.45 (br, m, 1H), 3.3 - 3.05 (br, m, 2H),

2.15 - 2.85 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.79 (t, 3H); ^{13}C NMR δ 195.0, 137.8, 134.5, 132.3, 131.6, 130.8, 128.8, 67.5, 53.7, 51.9, 31.4, 22.9, 17.2, 13.6; APCI MS m/z 300, 302, 304 ($M + 1$); Anal. ($\text{C}_{15}\text{H}_{20}\text{Cl}_3\text{NO}$) C, H, N, Cl.

1-(3,4-Dihydroxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrobromide (4v)

1-(3,4-Dimethoxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4w** (1.50 g, 4.6 mmol) was freed from its hydrochloride salt by treatment with aqueous Na_2CO_3 and extraction into CH_2Cl_2 . The organics were dried (MgSO_4), filtered, and reduced to a pale yellow oil *in vacuo*. The oil was taken up in CH_2Cl_2 (10 mL) and cooled to -78°C , whereon BBr_3 (46 mL, 1.0 M solution in CH_2Cl_2 , 46 mmol) was added dropwise over 0.5 h. The resulting yellow mixture was warmed slowly to room temperature and stirred for 3 h. The yellow solution was hydrolyzed cautiously with aq. Na_2CO_3 (20% solution) until the pH was 8, then water (50 mL) was added and the solution was allowed to stand overnight. Neutral organics were extracted from the mixture by separation of the CH_2Cl_2 layer, which was then discarded. The aqueous layer was acidified to pH 3 with 1 M HCl, most of the water was removed by rotary evaporation, and the remaining volume of ca. 10 mL was allowed to cool in the refrigerator. After 3 d, a white solid separated from the solution and was collected by filtration. Recrystallization ($\text{EtOH}/\text{Et}_2\text{O}$) afforded pure 1-(3,4-dihydroxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4v** as its hydrobromide, an off-white solid (0.60 g, 44%); Mp $181 - 182^\circ\text{C}$; ^1H NMR δ 10.42 (s, 1H), 10.1 - 9.9 (br, 1H), 9.59 (s, 1H), 7.51 (dd, 1H), 7.43 (d, 1H), 6.91 (d, 1H), 5.35 - 5.25 (br, 1H), 3.75 - 3.5 (br, 1H), 3.5 - 3.3 (br, 1H), 3.3 - 3.15 (br, 1H), 3.0 - 2.85 (br, 1H), 2.1 - 1.8 (m, 6H), 1.3 - 1.0 (m, 2H), 0.80 (t, 3H); ^{13}C NMR δ 194.8, 153.4, 146.4, 126.7, 123.5, 116.0, 115.9, 67.5, 54.5, 52.3, 32.8, 23.2, 17.9, 14.3; APCI MS m/z 264 ($M + 1$); Anal. ($\text{C}_{15}\text{H}_{22}\text{BrNO}_3$) C, H, N, Br.

1-(3,4-Dimethoxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4w)

2-Bromo-1-(3,4-dimethoxyphenyl)pentan-1-one **3w** was obtained together with 2-bromo-1-(2-bromo-4,5-dimethoxyphenyl)pentan-1-one by General Procedure B. The compounds were separated by flash column chromatography (10% EtOAc/hexane) to provide 2-bromo-1-(3,4-dimethoxyphenyl)pentan-1-one **3w**: ^1H NMR δ 7.66 (dd, 1H), 7.58 (d, 1H), 6.91 (d, 1H), 5.15 (dd, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 1.01 (t, 3H), and 2-bromo-1-(2-bromo-4,5-dimethoxyphenyl)pentan-1-one: ^1H NMR δ 7.07 (s, 1H), 7.04 (s, 1H), 5.28 (dd, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 2.3 - 2.0 (m, 2H), 1.7 - 1.4 (m, 2H), 1.00 (t, 3H). Compound **4w** was then prepared from **3w** as described in General Procedure C to provide a solid (74% yield); Mp 177°C (dec.); ^1H NMR δ 10.5 - 10.3 (br, 1H), 7.78 (d, 1H), 7.53 (d, 1H), 7.18 (d, 1H), 5.55 - 5.4 (br, m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.7 - 3.55 (br, m, 1H), 3.5 - 3.3 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.05 - 2.9 (br, m, 1H), 2.1 - 1.8 (m, 6H), 1.3 - 1.0 (m, 2H), 0.80 (t, 3H); ^{13}C NMR δ 194.7, 154.7, 149.0, 127.2, 124.6, 111.2, 110.5, 66.7, 56.0, 55.7, 53.7, 51.8, 32.1, 22.8, 17.4, 13.7; APCI MS m/z 292 ($M + 1$); Anal. ($\text{C}_{17}\text{H}_{26}\text{ClNO}_3$) C, H, N, Cl.

1-(4-Furan-2-ylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4x)

This compound was prepared using a procedure analogous to that described later for the preparation of **4z**, except that commercially available 2-tributylstannyl furan was employed as a starting material, and chromatography was not performed on the crude free base. The crude hydrochloride was recrystallized from hot EtOH to give pure **4x** as a colorless crystalline solid: (59% yield); Mp 236°C (dec.); ^1H NMR ($\text{DMSO}-d_6 + 6$ drops CD_3OD) δ 8.14 (d, 2H), 7.95 (d, 2H), 7.90 (d, 1H), 7.29 (d, 1H), 6.71 (dd, 1H), 5.51 (m, 1H), 3.7 - 3.6 (br, m, 1H), 3.6 - 3.45 (br, m, 1H), 3.35 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.15 - 1.85 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 1.0 (m, 1H), 0.81 (t, 3H); ^{13}C NMR δ 195.7, 151.8, 145.1, 136.0, 132.6, 130.0, 123.8, 112.9, 109.9, 67.8, 54.2, 52.0, 32.0, 22.9, 17.3, 13.7; APCI MS m/z 298 ($M + 1$); Anal. ($\text{C}_{19}\text{H}_{24}\text{ClNO}_2$) C, H, N, Cl.

2-Pyrrolidin-1-yl-1-(4-thiophen-2-yl-phenyl)pentan-1-one hydrochloride (4y)

This compound was prepared using a procedure analogous to that described later for the preparation of **4z**, except that commercially available 2-tributylstannyl thiophene was employed as a starting material, and chromatography was not performed on the crude free base. The crude hydrochloride was readily obtained by treatment of the crude free base with 2M ethereal HCl. Recrystallization from hot EtOH gave pure **4v** as a colorless crystalline solid (61% yield). Mp 220 °C (dec.); ¹H NMR (DMSO-d₆ + 12 drops CD₃OD) δ 8.12 (d, 2H), 7.93 (d, 2H), 7.77 (dd, 1H), 7.72 (dd, 1H), 7.23 (dd, 1H), 5.5 - 5.4 (br, 1H), 3.7 - 3.45 (br, m, 2H), 3.3 - 3.2 (br, m, 1H), 3.1 - 3.0 (br, m, 1H), 2.2 - 1.9 (br, m, 6H), 1.35 - 1.2 (m, 1H), 1.2 - 1.0 (m, 1H), 0.83 (t, 3H); ¹³C NMR δ 195.9, 141.8, 140.3, 132.9, 130.3, 129.3, 128.6, 126.6, 126.0, 68.1, 54.5, 52.1, 32.2, 23.1, 17.4, 13.8; APCI MS *m/z* 314 (M + 1); Anal. (C₁₉H₂₄ClNOS) C, H, N, Cl.

1-(4-N-Methylpyrrolephenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4z)

To a cooled (-78 °C) solution of *N*-methylpyrrole (1.14 g, 14 mmol) in THF (10 mL), ¹BuLi (9.1 mL of a 1.7M solution in pentane, 15 mmol) was added drop-wise. The mixture was then warmed to room temperature for 2 h, then cooled to -78 °C. Chlorotributylstannane (5.0 g, 15 mmol) was added to the mixture dropwise. On completion of addition, the mixture was warmed to room temperature and stirred for 1 h. The mixture was filtered and reduced to an oil *in vacuo*. This oil (crude 2-tributylstannyl-*N*-methylpyrrole) was added to a solution of 2-pyrrolidin-1-yl-1-(4-bromophenyl)-pentan-1-one (which had been freed from its hydrochloride **4f** by treatment with 20% aqueous Na₂CO₃ and extraction into Et₂O) in dioxane (30 mL). The resulting solution was degassed by purging with N₂. [Pd(PPh₃)₄] (264 mg, 0.22 mmol) was added and the mixture was heated to 95 - 100 °C (oil bath temperature) for a period of 10 h. The solvent was removed *in vacuo*. The pure free base was obtained by column chromatography (5% MeOH/CH₂Cl₂) as a yellow oil. The hydrochloride was prepared by treatment with 2M ethereal HCl. Lyophilization of an aqueous solution of the salt afforded 1-(4-*N*-methylpyrrolephenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride as a pale green solid **4z** (1.4 g, 36%). Mp 185 °C; ¹H NMR δ 10.6 - 10.45 (br, 1H), 8.11 (d, 2H), 7.72 (d, 2H), 7.00 (dd, 1H), 6.45 (dd, 1H), 6.15 (dd, 1H), 5.54 (m, 1H), 3.77 (s, 3H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.35 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.1 - 1.85 (br, m, 6H), 1.35 - 1.2 (m, 1H), 1.2 - 1.0 (m, 1H), 0.82 (t, 3H); ¹³C NMR δ 195.6, 139.1, 131.9, 131.5, 129.4, 127.4, 127.1, 111.1, 108.2, 67.2, 53.7, 51.9, 35.6, 31.9, 22.9, 17.4, 13.7; APCI MS *m/z* 311 (M + 1); Anal. (C₂₀H₂₇ClN₂O.2/3H₂O) C, H, N, Cl.

1-(4-Methylphenyl)pent-2-en-1-one (5a)

This compound was prepared as described below for **5b** employing 2-bromo-1-(4-methylphenyl)pentan-1-one **3a** as starting material (82% yield); ¹H NMR δ 7.85 (d, 2H), 7.25 (d, 2H), 7.10 (dt, 1H), 6.88 (dt, 1H), 2.39 (s, 3H), 2.32 (m, 2H), 1.13 (t, 3H); ¹³C NMR δ 190.3, 150.6, 143.2, 135.3, 129.0, 128.5, 124.7, 25.7, 21.5, 12.2.

1-(3,4-Dichlorophenyl)pent-2-en-1-one (5b)

2-Bromo-1-(3,4-dichlorophenyl) pentan-1-one, **3u**, (3.36 g, 10.9 mmol) was dissolved in DMF (60 mL). Li₂CO₃ (1.28 g, 17 mmol) and LiBr (0.99 g, 11.5 mmol) were added to the solution, which was then heated with stirring to 110 - 120 °C (oil bath temperature) for 1.5 h. The mixture was diluted with H₂O (100 mL) and the organics were extracted into EtOAc (3 × 50 mL). The ethyl acetate layer was collected and washed with saturated brine (2 × 50 mL), dried (MgSO₄), filtered, and reduced to an oil *in vacuo*. Flash column chromatography (1% EtOAc/hexane to 2.5% EtOAc/hexane) furnished pure **5b** as a colorless solid (1.5 g, 60%). ¹H NMR δ 8.01 (d, 1H), 7.76 (dd, 1H), 7.55 (d, 1H), 7.15 (dt, 1H), 6.80 (dt, 1H), 2.37 (m, 2H), 1.15 (t, 3H); ¹³C NMR δ 188.5, 152.8, 137.6, 137.1, 133.2, 130.6, 130.5, 127.5, 124.1, 26.0, 12.2.

1-(3,4-Dichlorophenyl)-3-pyrrolidin-1-yl-pentan-1-one hydrochloride (6b)

1-(3,4-Dichlorophenyl)pent-2-en-1-one **5b** (1.29 g, 5.63 mmol) was taken up in EtOH (10 mL), cooled on an ice bath, and degassed by purging with N₂. Pyrrolidine (0.80 g, 11 mmol) was added dropwise over 2 min. After 0.5 h, the ethanolic solution was separated between 1M aqueous HCl and Et₂O. The HCl extracts were collected and back-extracted into Et₂O by treatment with 20% aqueous Na₂CO₃. The ethereal extracts were dried (MgSO₄), filtered, and treated with 2M ethereal HCl. Trituration afforded 1-(3,4-dichlorophenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride **6b** as a white powder which was filtered and washed copiously with Et₂O (0.99 g, 50%); Mp 104 – 107 °C (dec.); ¹H NMR δ 11.1 - 10.9 (br, 1H), 8.27 (d, 1H), 7.98 (dd, 1H), 7.87 (d, 1H), 3.9 - 3.35 (br, m, 5H), 3.15 - 2.95 (br, 2H), 2.05 - 1.8 (br, m, 5H), 1.8 - 1.6 (m, 1H), 0.90 (t, 3H); ¹³C NMR δ 195.0, 136.4, 136.1, 131.8, 131.1, 130.3, 128.1, 59.2, 50.7, 50.1, 38.2, 23.8, 22.9, 10.0; APCI MS *m/z* 300, 302, 304 (M + 1); Anal. (C₁₅H₂₀Cl₃NO.1/3H₂O) C, H, N, Cl.

1-(4-Methylphenyl)-3-pyrrolidin-1-yl-pentan-1-one hydrochloride (6a)

This compound was prepared from 1-(4-methylphenyl)-2-en-1-one **5a** using the same procedure as that described for **6b**. Mp 97 °C (dec.); ¹H NMR δ 11.1 - 10.9 (br, 1H), 7.94 (d, 2H), 7.38 (d, 2H), 3.9 - 3.75 (br, 1H), 3.7 - 3.6 (m, 1H), 3.6 - 3.3 (m, 3H), 3.15 - 2.95 (br, m, 2H), 1.96 (s, 3H), 2.0 - 1.8 (br, m, 5H), 1.8 - 1.6 (m, 1H), 0.88 (t, 3H); ¹³C NMR δ 196.2, 144.3, 133.5, 129.3, 128.3, 59.7, 50.7, 50.4, 37.9, 23.8, 22.9, 22.8, 21.2, 9.9; APCI MS *m/z* 246 (M + 1); Anal. (C₁₆H₂₄ClNO) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride (7b)

2-Bromo-1-(3,4-dichlorophenyl)pentan-1-one **3u** (3.5 g, 15 mmol), pyrrolidine.HCl (2.4 g, 23 mmol) and paraformaldehyde (1.35 g, 45 mmol) were taken up in ⁱPrOH (25 mL) containing concentrated HCl (0.2 mL). The mixture was brought to reflux for 16 h. The solvent was removed by rotary evaporation and the residue was separated between 1 M aqueous HCl and Et₂O. The aqueous extracts were basified with 20% aqueous Na₂CO₃ to pH 8–9 and the organics were extracted into Et₂O. The organics were dried (MgSO₄), filtered, and reduced to an oil *in vacuo*. Column chromatography (10% MeOH/CH₂Cl₂) gave the pure free base. Reaction with 2 M ethereal HCl and filtration of the resulting white precipitate provided 1-(3,4-dichlorophenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride, **7b** (0.61 g, 12%). Mp 168 °C (dec.); ¹H NMR δ 10.7 - 10.5 (br, 1H), 8.29 (d, 1H), 8.05 (dd, 1H), 7.88 (d, 1H), 4.3 - 4.1 (br, 1H), 3.7 - 3.5 (br, m, 2H), 3.5 - 3.25 (br, m, 2H), 3.15 - 2.85 (br, m, 2H), 2.1 - 1.75 (br, m, 4H), 1.75 - 1.4 (m, 2H), 1.35 - 1.05 (m, 2H), 0.81 (t, 3H); ¹³C NMR δ 198.9, 136.6, 135.9, 132.1, 131.4, 131.2, 130.5, 130.3, 128.7, 128.5, 54.1, 53.4, 42.3, 42.2, 33.1, 22.7, 22.4, 18.8, 13.8; APCI MS *m/z* 314, 312, 310 (M + 1); Anal. (C₁₆H₂₂Cl₃NO) C, H, N, Cl.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride (7a)

This compound was prepared from 1-(2-methylphenyl)pentan-1-one (3.5 g, 20 mmol) using the same method as described for **7b** with the following modifications. No chromatography was performed. The hydrochloride salt of the crude free base was isolated after extraction of the crude reaction mixture into 1 M aqueous HCl, and back extraction (with 20% aqueous Na₂CO₃) into Et₂O, followed by acidification with 2M HCl in Et₂O. The product was recrystallized from EtOH/Et₂O to give pure crystalline 1-(4-methylphenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride **7a** (2.6 g, 44%). Mp 176 °C (dec.); ¹H NMR δ 10.8 - 10.6 (br, 1H), 7.98 (d, 2H), 7.39 (d, 2H), 4.25 - 4.15 (br, m, 1H), 3.65 - 3.5 (m, 2H), 3.5 - 3.25 (m, 2H), 3.1 - 2.95 (br, m, 1H), 2.95 - 2.8 (br, m, 1H), 2.40 (s, 3H), 2.0 - 1.75 (m, 4H), 1.7 - 1.4 (m, 2H), 1.3 - 1.1 (m, 2H), 0.81 (t, 3H); ¹³C NMR δ 200.4, 144.4, 135.2, 129.7, 129.5, 128.7, 128.5, 54.0, 53.7, 53.3, 41.9, 33.5, 22.8, 22.3, 21.1, 19.0, 13.8; APCI MS *m/z* 260 (M + 1); Anal. (C₁₇H₂₆ClNO) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-pyrrolidin-1-yl-butan-1-one hydrochloride (9a)

1-(3,4-Dichlorophenyl)butan-1-one, prepared in quantitative yield from 3,4-dichlorobenzonitrile and *n*-PrMgCl (General Procedure A); ¹H NMR δ 8.01 (d, 1H), 7.78 (dd, 1H), 7.54 (d, 1H), 2.91 (t, 2H), 1.77 (sextet, 2H), 1.01 (t, 3H), was brominated according to General Procedure B to give 2-bromo-1-(3,4-dichlorophenyl)butan-1-one; ¹H NMR δ 8.09 (d, 1H), 7.84 (dd, 1H), 7.57 (d, 1H), 4.95 (dd, 1H), 2.35 - 2.05 (m, 2H), 1.09 (t, 3H). Compound **9a** was prepared according to General Procedure C (71% yield); Mp 211 °C (dec.); ¹H NMR δ 10.95 - 10.75 (br, 1H), 8.35 (d, 1H), 8.06 (dd, 1H), 7.92 (d, 1H), 5.75 - 5.65 (br, m, 1H), 3.65 - 3.35 (br, m, 2H), 3.3 - 3.1 (br, m, 2H), 2.15 - 1.9 (br, m, 6H), 0.78 (t, 3H); ¹³C NMR δ 194.7, 137.7, 134.5, 132.3, 131.6, 130.7, 128.8, 68.5, 53.7, 51.8, 23.0, 22.6, 8.4; APCI MS *m/z* 286, 288, 290 (M + 1); Anal. (C₁₄H₁₈Cl₃NO) C, H, N.

4-Methyl-2-pyrrolidin-1-yl-1-(4-methylphenyl)pentan-1-one hydrochloride (9b)

4-Methyl-1-(4-methylphenyl)pentan-1-one, prepared in quantitative yield by Friedel-Crafts acylation of toluene with 4-methylvaleroyl chloride: ¹H NMR δ 7.86 (d, 2H), 7.26 (d, 2H), 3.94 (t, 2H), 2.41 (s, 3H), 1.62 (m, 3H), 0.94 (d, 6H) was converted to 2-bromo-4-methyl-1-(4-methylphenyl)pentan-1-one, as described in General Procedure B: ¹H NMR δ 7.92 (d, 2H), 7.29 (d, 2H), 5.21 (dd, 1H), 2.43 (s, 3H), 2.15 - 1.95 (m, 2H), 1.95 - 1.75 (m, 1H), 0.96 (d, 6H). 4-Methyl-2-pyrrolidin-1-yl-1-(4-methylphenyl)pentan-1-one hydrochloride **9b** was then prepared as described in General Procedure C (68% yield); Mp 218 °C (dec.); ¹H NMR δ 10.9 - 10.75 (br, 1H), 8.06 (d, 2H), 7.45 (d, 2H), 5.46 (m, 1H), 3.75 - 3.6 (br, 1H), 3.6 - 3.4 (br, 1H), 3.3 - 3.0 (br, m, 2H), 2.42 (s, 3H), 2.1 - 1.7 (m, 6H), 1.45 - 1.3 (m, 1H), 0.82 (dd, *J* = 2, 6 Hz, 6H); ¹³C NMR δ 197.2, 164.0, 132.9, 129.9, 129.0, 64.4, 52.7, 51.2, 24.2, 23.3, 22.8, 21.5, 21.3; APCI MS *m/z* 260 (M + 1); Anal. (C₁₇H₂₆ClNO) C, H, N, Cl.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pent-4-ene-1-one hydrochloride (9c)

This compound was prepared as described previously.²⁹ Mp 196 °C (dec.); ¹H NMR δ 10.8 - 10.6 (br, 1H), 7.96 (d, 2H), 7.43 (d, 2H), 5.8 - 5.6 (m, 2H), 5.03 (s, 1H), 5.00 (m, 1H), 3.75 - 3.6 (br, 1H), 3.6 - 3.4 (br, 1H), 3.4 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 3.85 - 3.65 (br, m, 2H), 2.42 (s, 3H), 2.2 - 1.85 (br, m, 4H); ¹³C NMR δ 195.2, 145.8, 131.8, 130.6, 129.7, 129.0, 120.1, 66.9, 53.8, 52.0, 34.2, 22.9, 21.3; APCI MS *m/z* 244 (M + 1); Anal. (C₁₆H₂₂ClNO) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-pyrrolidin-1-yl-pent-4-ene-1-one hydrochloride (9d)

This compound was prepared as described for **9c**.²⁹ Mp 176 °C (dec.); ¹H NMR δ 10.8 - 10.6 (br, 1H), 8.29 (d, 1H), 8.00 (dd, 1H), 7.94 (d, 1H), 5.8 - 5.6 (m, 2H), 5.07 (s, 1H), 5.02 (m, 1H), 3.75 - 3.6 (br, m, 1H), 3.6 - 3.3 (br, m, 1H), 3.3 - 3.1 (br, m, 2H), 2.77 (m, 2H), 2.2 - 1.8 (br, m, 4H); ¹³C NMR δ 194.2, 137.8, 134.4, 132.2, 131.6, 130.8, 130.3, 128.8, 120.6, 67.2, 53.9, 52.1, 33.8, 22.9; APCI MS *m/z* 302 ((M + 1), 100%), 300, 298; Anal. (C₁₅H₁₈Cl₃NO) C, H, N, Cl.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pent-4-yn-1-one hydrochloride (9e)

1-(4-Methylphenyl)-2-pyrrolidin-1-ylethanone **8**²⁹ (25 g, 104 mmol) was freed from its hydrochloride by treatment with aqueous Na₂CO₃ and extraction into Et₂O. The organics were dried (MgSO₄), filtered and reduced *in vacuo* to a yellow oil. This oil was taken up in toluene (200 mL), and NaNH₂ was added to the stirring solution, which was then heated to approximately 120 °C (oil bath temperature) for 0.5 h. The solution was allowed to cool to about 100 °C and propargyl bromide (13 mL, 80% w/w solution in toluene, 14 g, 115 mmol) was added to the orange mixture at such a rate that steady reflux was maintained with concomitant NH₃ evolution. Upon complete addition (0.5 h), the mixture was allowed to cool to room temperature and was then hydrolyzed cautiously by addition of water (100 mL). The

toluene layer was separated and the aqueous layer was extracted with toluene (2 × 50 mL). The combined organics were dried (MgSO₄), filtered and reduced *in vacuo* to a brown oil that was taken up in Et₂O (50 mL). 2 M HCl in Et₂O was added to the ethereal solution of the oil.

Trituration afforded a brown solid that could not be crystallized from EtOH/Et₂O. The solvents were removed *in vacuo* and the free base was prepared by addition of 2 M NaOH solution until pH 8–9. The organics were extracted into Et₂O (3 × 100 mL) to give a light brown solution. Back-extraction into 1 M HCl (3 × 50 mL) gave a light yellow solution. The water was removed by rotary evaporation; lyophilization than gave a light brown gum (5.3 g). Recrystallization from EtOH/Et₂O afforded pure 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pent-4-yn-1-one hydrochloride **9e** (3.15 g, 11%): Mp 178 °C (dec.); ¹H NMR δ 10.6 - 10.4 (br, 1H), 7.97 (d, 2H), 7.45 (d, 2H), 5.66 (m, 1H), 3.7 - 3.2 (m, 3H), 3.2 - 2.9 (m, 4H), 2.43 (s, 3H), 2.1 - 1.8 (m, 4H); ¹³C NMR δ 193.9, 146.0, 131.1, 129.7, 129.2, 76.8, 76.6, 65.2, 54.0, 52.0, 22.9, 22.9, 21.3, 20.0; APCI MS *m/z* 242 (M + 1); Anal. (C₁₆H₂₀ClNO) C, H, N, Cl.

2-Butylamin-1-yl-1-(3,4-dichlorophenyl)pentan-1-one hydrochloride (9f)

Compound **9f** (an off-white solid) was obtained from **3u** (described above) and *n*-butylamine, according to General Procedure C (71% yield); Mp 185 °C (dec.); ¹H NMR δ 9.8 - 9.6 (br, 1H), 9.3 - 9.1 (br, 1H), 8.35 (d, 1H), 8.04 (dd, 1H), 7.91 (d, 1H), 5.4 - 5.25 (br, 1H), 3.05 - 2.75 (br, m, 2H), 2.05 - 1.8 (br, m, 2H), 1.8 - 1.6 (br, m, 2H), 1.4 - 1.2 (m, 3H), 1.2 - 1.0 (m, 1H), 0.88 (t, 3H), 0.78 (t, 3H); ¹³C NMR δ 194.8, 137.6, 134.3, 132.3, 131.5, 130.6, 128.7, 60.8, 45.7, 31.5, 27.4, 19.3, 17.2, 13.6, 13.5; APCI MS *m/z* 302, 304, 306 (M + 1); Anal. (C₁₅H₂₂Cl₃NO) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-piperidin-1-yl-pentan-1-one hydrochloride (9g)

Compound **9g** was prepared from **3u** (described above) and piperidine, as described in General Procedure C (35% yield); Mp 202 °C (dec.); ¹H NMR δ 10.5 - 10.3 (br, 1H), 8.40 (d, 1H), 8.10 (dd, 1H), 7.94 (d, 1H), 5.45 - 5.35 (br, m, 1H), 3.7 - 3.55 (br, m, 1H), 3.45 - 3.3 (br, m, 1H), 3.2 - 1.95 (br, m, 2H), 2.1 - 1.65 (br, m, 7H), 1.5 - 1.3 (br, 1H), 1.2 - 1.0 (br, m, 2H), 0.81 (t, 3H); ¹³C NMR δ 195.3, 138.0, 135.3, 132.4, 131.6, 130.7, 128.8, 65.8, 52.0, 50.2, 29.3, 22.3, 22.0, 21.5, 17.8, 13.7; APCI MS *m/z* 314, 316, 318 (M + 1); Anal. (C₁₆H₂₂Cl₃NO) C, H, N, Cl.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-ol hydrochloride (diastereoisomers 9h and 9j)

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride **4a** (1.50 g, 5.32 mmol) was suspended in THF (20 mL). LiAlH₄ (0.20 g, 5.3 mmol) was added in several small portions at room temperature to the stirring mixture with slight heat evolution. The resulting clear solution was hydrolyzed cautiously with H₂O, then made acidic by addition of 1M aqueous HCl. The aqueous extracts were collected and basified to pH 8–9 with 20% aqueous Na₂CO₃. The organics were extracted into Et₂O, dried (MgSO₄), filtered, and reduced to an oil *in vacuo*. Chromatography (5% NEt₃/15% EtOAc/80% hexane) gave the two diastereoisomers **9h** and **9j**. The hydrochlorides were prepared from 2M ethereal HCl and recrystallized from EtOH/Et₂O to afford 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-ol hydrochloride **9h**, a colorless crystalline solid (0.57 g, 37%); Mp 140 - 142 °C; ¹H NMR δ 10.15 - 10.0 (br, 1H), 7.32 (d, 2H), 7.19 (d, 2H), 6.20 (d, *J* = 5 Hz, 1H), 5.24 (s, 1H), 3.75 - 3.65 (br, m, 1H), 3.65 - 3.5 (br, m, 1H), 3.4 - 3.3 (br, 2H), 3.2 - 3.05 (br, m, 1H), 2.30 (s, 3H), 2.1 - 1.8 (br, m, 4H), 1.75 - 1.6 (m, 1H), 1.4 - 1.25 (br, m, 1H), 1.1 - 0.95 (m, 1H), 0.8 - 0.6 (m, 1H), 0.57 (t, 3H); ¹³C NMR δ 138.3, 136.2, 128.6, 125.5, 69.3, 68.1, 51.5, 26.5, 22.7, 22.5, 20.7, 20.3, 13.7; APCI MS *m/z* 248 (M + 1); Anal. (C₁₆H₂₆ClNO) C, H, N, Cl. and 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-ol hydrochloride **9j**, a colorless microcrystalline solid (159 mg, 10%), this was the more polar material; Mp 219 °C (dec.); ¹H NMR δ 9.8 - 9.65 (br, 1H), 7.33 (d, 2H), 7.20 (d, 2H), 6.53 (d, *J* = 4 Hz, 1H), 4.65 (dd *J* = 4, 9 Hz, 1H), 3.55 - 3.3 (m, 3H), 3.3 - 3.15 (br, m,

1H), 3.15 - 2.95 (br, m, 1H), 2.31 (s, 3H), 2.0 - 1.85 (br, 4H), 1.55 - 1.35 (br, m, 2H), 1.05 - 0.85 (m, 1H), 1.75 - 1.6 (m, 4H); ^{13}C NMR δ 138.4, 137.3, 128.9, 127.1, 72.1, 67.0, 40.3, 40.1, 27.6, 23.3, 23.0, 20.8, 20.0, 13.6; APCI MS m/z 248 (M + 1); Anal. ($\text{C}_{16}\text{H}_{26}\text{ClNO}$) C, H, N, Cl.

Biological Procedures

(Provided by NIDA from Oregon Health & Science University and SRI International).

Unknowns were weighed and dissolved in DMSO to make a 10 mM stock solution. An initial dilution to 50 μM in assay buffer for binding, or to 1 mM in assay buffer for uptake, was made. Subsequent dilutions were made with assay buffer supplemented with DMSO, maintaining a final concentration of 0.1% DMSO. Pipetting was conducted using a Biomek 2000 robotic workstation.

Inhibition of Radioligand Binding of [^{125}I]RTI 55 to hDAT, hSERT or hNET in Clonal Cells

Cell preparation: HEK293 cells expressing hDAT, hSERT or hNET inserts are grown to 80% confluence on 150 mm diameter tissue culture dishes and serve as the tissue source. Cell membranes are prepared as follows. Medium is poured off the plate, and the plate is washed with 10 ml of calcium- and magnesium-free phosphate-buffered saline. Lysis buffer (10 ml; 2 mM HEPES with 1 mM EDTA) is added. After 10 min, cells are scraped from plates, poured into centrifuge tubes, and centrifuged $30,000 \times g$ for 20 min. The supernatant fluid is removed, and the pellet is resuspended in 12–32 ml of 0.32 M sucrose using a Polytron at setting 7 for 10 sec. The resuspension volume depends on the density of binding sites within a cell line and is chosen to reflect binding of 10% or less of the total radioactivity. Assay conditions: Each assay tube contains 50 μl of membrane preparation (about 10–15 μg of protein), 25 μl of unknown, compound used to define non-specific binding, or buffer (Krebs-HEPES, pH 7.4; 122 mM NaCl, 2.5 mM CaCl_2 , 1.2 mM MgSO_4 , 10 μM pargyline, 100 μM tropolone, 0.2% glucose and 0.02% ascorbic acid, buffered with 25 mM HEPES), 25 μl of [^{125}I]RTI-55 (40–80 pM final concentration) and additional buffer sufficient to bring up the final volume to 250 μl . Membranes are preincubated with unknowns for 10 min prior to the addition of the [^{125}I]RTI-55. The assay tubes are incubated at 25°C for 90 min. Binding is terminated by filtration over GF/C filters using a Tomtec 96-well cell harvester. Filters are washed for six seconds with ice-cold saline. Scintillation fluid is added to each square and radioactivity remaining on the filter is determined using a Wallac μ - or beta-plate reader. Specific binding is defined as the difference in binding observed in the presence and absence of 5 μM mazindol (HEK-hDAT and HEK-hNET) or 5 μM imipramine (HEKhSERT). Two or three independent competition experiments are conducted with duplicate determinations. GraphPAD Prism is used to analyze the ensuing data, with IC_{50} values converted to K_i values using the Cheng-Prusoff equation ($K_i = \text{IC}_{50} / (1 + ([\text{RTI-55}] / K_d \text{ RTI-55}))$).

Filtration Assay for Inhibition of [^3H]Neurotransmitter Uptake in HEK293 Cells Expressing Recombinant Biogenic Amine Transporters

Cell preparation: Cells are grown to confluence as described above. The medium is removed, and cells are washed twice with phosphate buffered saline (PBS) at room temperature. Following the addition of 3 ml Krebs-HEPES buffer, the plates are warmed in a 25°C water bath for 5 min. The cells are gently scraped and then triturated with a pipette. Cells from multiple plates are combined. One plate provides enough cells for 48 wells, which is required to generate data on two complete curves for the unknowns.

Uptake inhibition assay conditions: The assay is conducted in 96 1-ml vials. Krebs- HEPES (350 μl) and unknowns, compounds used to define non-specific uptake, or buffer (50 μl) are added to vials and placed in a 25°C water bath. Specific uptake is defined as the difference in uptake observed in the presence and absence of 5 μM mazindol (HEK-hDAT and HEK-hNET)

or 5 μ M imipramine (HEK-hSERT). Cells (50 μ l) are added and preincubated with the unknowns for 10 min. The assay is initiated by the addition of [3 H]dopamine, [3 H]serotonin, or [3 H]norepinephrine (50 μ l, 20 nM final concentration). Filtration through Whatman GF/C filters presoaked in 0.05% polyethylenimine is used to terminate uptake after 10 min. The IC₅₀S are calculated applying the GraphPAD Prism program to triplicate curves made up of 6 drug concentrations each. Two or three independent determinations of each curve are made.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Schildkraut JJ. The catecholamine hypothesis of affective disorders: A review of supporting evidence. *J. Psychiatry* 1965;122:509–522.
2. Madras BK, Pristupa ZB, Niznik HB, Liang AY, Blundell P, Gonzalez MD, Meltzer PC. Nitrogen-based drugs are not essential for blockade of monoamine transporters. *Synapse* 1996;24:340–348. [PubMed: 10638825]
3. Biederman J, Spencer T. Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. *Biol. Psychiatr* 1999;46:1234–1242.
4. Popper CW. Pharmacologic alternatives to psychostimulants for the treatment of attention-deficit/hyperactivity disorder. *Child Adolesc. Psychiatr. Clin. N Am* 2000;9:605–646. [PubMed: 10944659]
5. Fleckenstein AE, Gibb JW, Hanson GR. Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. *Eur. J. Pharmacol* 2000;406:1–13. [PubMed: 11011026]
6. Gorelick DA, Gardner EL, Xi ZX. Agents in development for the management of cocaine abuse. *Drugs* 2004;64:1547–1573. [PubMed: 15233592]
7. Gainetdinov RR, Caron MG. Monoamine transporters: from genes to behavior. *Ann. Rev. Pharm. and Tox* 2002;43:261–284.
8. Vocci FJ, Acri J, Elkashef A. Medications development for addictive disorders: the state of the science. *Am. J. Psychiatry* 2005;162:1432–1440. [PubMed: 16055764]
9. Coyle JT, Snyder SH. Antiparkinsonian drugs: inhibition of dopamine uptake in the corpus striatum as a possible mechanism of action. *Science* 1969;166:899. [PubMed: 5345207]
10. Iversen, LL. Uptake process of biogenic amines. New York: Plenum; 1975. p. 381-442.
11. Meltzer PC, Blundell P, Madras BK. Structure activity relationships of inhibition of the dopamine transporter by 3-aryl bicyclo[3.2.1]octanes. *Med. Chem. Res* 1998;8:12–34.
12. Meltzer PC, Wang B, Chen Z, Blundell P, Jayaraman M, Gonzalez MD, George C, Madras BK. Synthesis of 6- and 7-hydroxy-8-azabicyclo[3.2.1]octanes and their binding affinity for the dopamine and serotonin transporters. *J. Med. Chem* 2001;44:2619–2635. [PubMed: 11472216]
13. Meltzer PC, Liu S, Blanchette HS, Blundell P, Madras BK. Design and synthesis of an irreversible dopamine-sparing cocaine antagonist. *Bioorg. & Med. Chem* 2002;10:3583–3591. [PubMed: 12213473]
14. Madras BK, Fahey MA, Miller GM, De La Garza R, Goulet M, Spealman RD, Meltzer PC, George SR, O'Dowd BF, Bonab E, Livni E, Fischman AJ. Non-amine-based dopamine transporter (reuptake) inhibitors retain properties of amine-based progenitors. *Eur J Pharmacol* 2003;479:41–51. [PubMed: 14612136]

15. Kennedy LT, Hanbauer J. Sodium sensitive cocaine binding to rat striatal membrane: possible relationship to dopamine uptake sites. *J. Neurochem* 1983;34:1137-1144.
16. Schoemaker H, Pimoule C, Arbilla S, Scatton B, Javoy-Agid F, Langer SZ. Sodium dependent [³H] cocaine binding associated with dopamine uptake sites in the rat striatum and human putamen decrease after dopaminergic denervation and in Parkinson's disease. *Naunyn-Schmiedeberg's Arch. Pharmacol* 1985;329:227-235. [PubMed: 3927176]
17. Reith MEA, Meisler BE, Sershen H, Lajtha A. Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. *Biochem. Pharmacol* 1986;35:1123-1129. [PubMed: 3964292]
18. Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* 1987;237:1219-1223. [PubMed: 2820058]
19. Madras BK, Fahey MA, Bergman J, Canfield DR, Spealman RD. Effects of cocaine and related drugs in nonhuman primates: I. [³H]Cocaine binding sites in caudate-putamen. *J. Pharmacol. Exp. Ther* 1989;251:131-141. [PubMed: 2529364]
20. Bergman J, Madras BK, Johnson SE, Spealman RD. Effects of cocaine and related drugs in nonhuman primates. III. Self-administration by squirrel monkeys. *J. Pharmacol. Exp. Ther* 1989;251:150-155. [PubMed: 2529365]
21. Canfield DR, Spealman RD, Kaufman MJ, Madras BK. Autoradiographic localization of cocaine binding sites by [³H]CFT ([³H]WIN 35,428) in the monkey brain. *Synapse* 1990;6:189-195. [PubMed: 2237780]
22. Madras BK, Kamien JB, Fahey M, Canfield D, Milius RA, Saha JK, Neumeyer JL, Spealman RD. N-Modified fluorophenyltropane analogs of cocaine with high affinity for [³H]cocaine receptors. *Pharmacol Biochem. Behav* 1990;35:949-953. [PubMed: 2345768]
23. Kaufman MJ, Madras BK. Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's diseased striatum. *Synapse* 1991;9:43-49. [PubMed: 1796351]
24. Kuhar MJ, Ritz MC, Boja JW. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci* 1991;14:299-302. [PubMed: 1719677]
25. Servin A, Jacquot CN, Rapin JR. Effects of pyrovalerone on peripheral noradrenergic mechanisms. *Biochem. Pharmacol* 1978;27:1693-1694. [PubMed: 29644]
26. Perrine DM, Ross JT, Nervi SJ, Zimmerman RH. A short, one-pot synthesis of bupropion. *J. Chem. Ed* 2000;77:1479-1480.
27. Musso DL, Mehta NB, Soroko FE, Ferris RM, Hollingsworth EB, Kenney BT. Synthesis and evaluation of the antidepressant activity of the enantiomers of bupropion. *Chirality* 1993;5:495-500. [PubMed: 8240925]
28. Lancelot JC, Robba M, Bonnet JJ, Vaugeois JM, Costentin J. Synthesis and preliminary study of the activity of thiophene analogues of pyrovalerone on the neuronal uptake of the monoamines. *Eur. J. Med. Chem* 1992;27:297-300.
29. Heffe W. Die Stevens-umlagerung von allyl-phenacyl-ammoniumsalzen. *Helv. Chim. Acta* 1964;47:1289-1292.
30. Stille G, Ackermann H, Eichenberger E, Lauener H. Vergleichende pharmakologische untersuchung eines sentralem stimulans 1-p-tolyl-1-oxo-2-pyrrolidino-n-pentan-HCl. *Arzneimittle-Forsch* 1963;13:871-877. [PubMed: 14198718]
31. Holliday AR, Morris RB, Sharpley RP. Compound 84/F 1983 compare with D-amphetamine and placebo in regard to effects on human performance. *Psychopharmacologia* 1964;6:192-200. [PubMed: 4378595]
32. Gardos G, Cole JO. Evaluation of pyrovalerone in chronically fatigued volunteers. *Current Therap. Res* 1971;13:631-635.
33. Fauquet J-P, Morel E, Demarty C, Rapin JR. Role des catecholamines centrales dans l'activite psychostimulante de la pyrovalerone. *Arch. Int. Pharmacodyn* 1976;224:325-337. [PubMed: 1035081]
34. Vaugeois J-M, Bonnet J-J, Duterte-Boucher D, Costentin J. In vivo occupancy of the striatal dopamine uptake complex by various inhibitors does not predict their effects on locomotion. *Eur. J. Pharm* 1993;230:195-201.

35. Michaelis W, Russel JH, Schindler O. The metabolism of pyrovalerone hydrochloride. *J. Med. Chem* 1970;13:497–503. [PubMed: 5441133]
36. Eshleman AJ, Carmolli M, Cumbay M, Martens CR, Neve KA, Janowsky A. Characteristics of drug interactions with recombinant biogenic amine transporters expressed in the same cell type. *J Pharmacol Exp Ther* 1999;289:877–885. [PubMed: 10215666]
37. Calligaro DO, Eldefrawi ME. High affinity stereospecific binding of [³H]cocaine in striatum and its relationship to the dopamine transporter. *Membr. Biochem* 1987;7:87–106. [PubMed: 3454391]
38. Glennon RA, Young R, Martin BR, Dal Cason TA. Methcathione ("cat"): an enantiomeric potency comparison. *Pharmacol. Biochem. Behav* 1995;50:601–606. [PubMed: 7617707]
39. Carroll FI, Gao Y, Rahman MA, Abraham P, Parham K, Lewin AH, Boja JW, Kuhar MJ. Synthesis, ligand binding, QSAR, and CoMFA study of 3β-(p-substituted phenyl)tropane-2β-carboxylic acid methyl esters. *J. Med. Chem* 1991;34:2719–2725. [PubMed: 1895292]
40. Newman AH, Izenwasser S, Robarge MJ, Kline RH. CoMFA study of novel phenyl ring-substituted 3α-(diphenylmethoxy)tropane analogues at the dopamine transporter. *J. Med. Chem* 1999;42:3502–3350. [PubMed: 10479283]
41. Deutsch HM. Structure-activity relationships for methylphenidate analogs and comparisons to cocaine and tropanes. *Med. Chem. Res* 1998;8:91–99.
42. Meltzer PC, Wang P, Blundell P, Madras BK. Synthesis and evaluation of dopamine and serotonin transporter inhibition by oxacyclic and carbacyclic analogues of methylphenidate. *J. Med. Chem* 2003;46:1538–1545. [PubMed: 12672255]
43. Newman AH. Novel dopamine transporter ligands: The state of the art. *Med. Chem. Res* 1998;8:1–11.
44. Carroll FI, Howell LL, Kuhar MJ. Pharmacotherapies for treatment of cocaine abuse: preclinical aspects. *J. Med. Chem* 1999;42:2721–2736. [PubMed: 10425082]
45. Carroll FI. 2002 medicinal chemistry division award address: Monoamine transporters and opioid receptors. Targets for addiction therapy. *J. Med. Chem* 2003;46:1775–1794. [PubMed: 12723940]
46. Deutsch HM, Collard DM, Zhang L, Burnham KS, Deshpande AK, Holtzman SG, Schweri MM. Synthesis and pharmacology of site-specific cocaine abuse treatment agents: 2-(aminomethyl)-3-phenylbicyclo[2.2.2]- and -[2.2.1]alkane dopamine uptake inhibitors. *J. Med. Chem* 1999;42:882–895. [PubMed: 10072685]
47. Carroll FI, Pawlusch N, Kuhar MJ, Pollard GT, Howard JL. Synthesis, monoamine transporter binding properties, and behavioral pharmacology of a series of 3β-(substituted phenyl)-2β-(3'-substituted isoxazol-5-yl)tropanes. *J. Med. Chem* 2004;47:296–302. [PubMed: 14711303]
48. Meltzer PC, Madras BK. Unpublished data

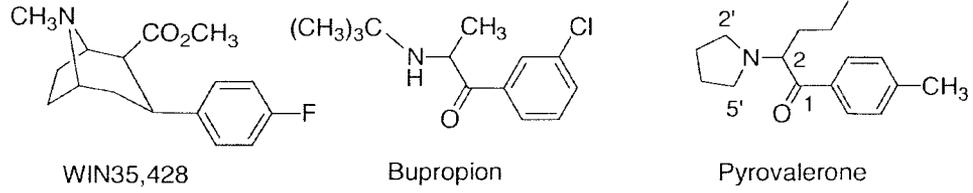
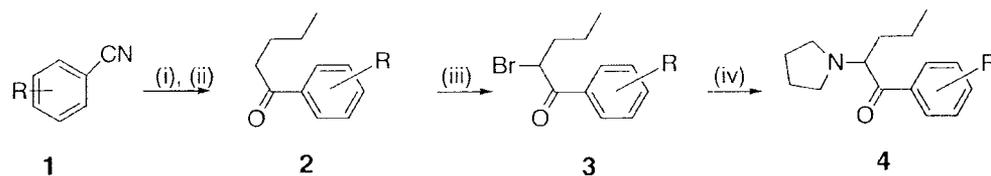


Figure 1.

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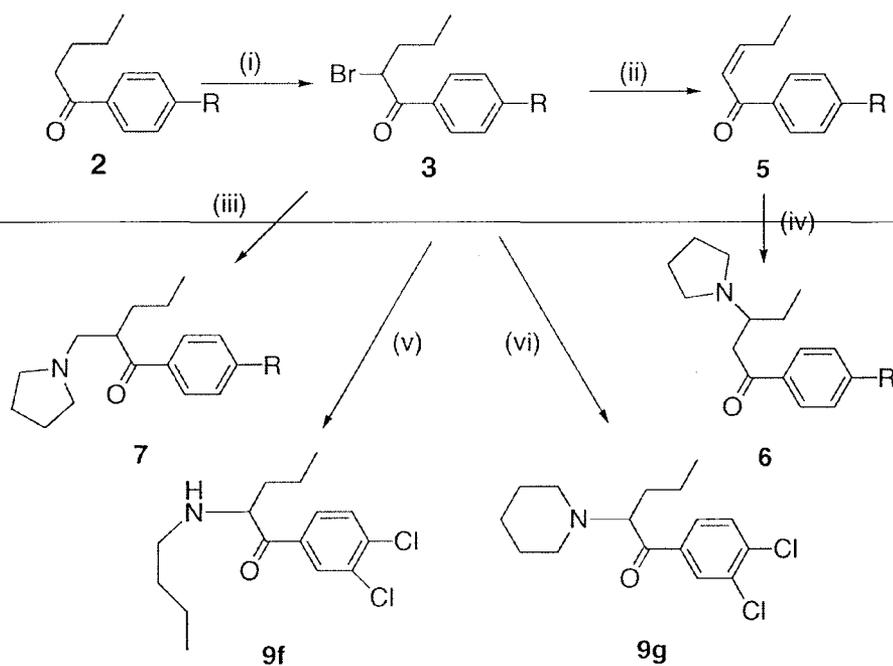
a R = 4-CH ₃ (R/S)	f R = 4-Br	k R = 4-OH	p R = 4-CF ₃	u R = 3,4-Cl ₂
b R = 4-CH ₃ (S)	g R = 4-I	l R = 4-NO ₂	q R = 4-CCCH ₃	v R = 3,4-(OH) ₂
c R = 4-CH ₃ (R)	h R = 3-I	m R = 4-OCH ₃	r R = 2-CH ₃	w R = 3,4-(OCH ₃) ₂
d R = H	i R = 4-CN	n R = 4-CO ₂ CH ₃	s R = 3-CH ₃	x R = 4-(2-Furan)
e R = 4-F	j R = 4-CH ₂ OH	o R = 4-NHCOCH ₃	t R = Naphthyl	y R = 4-(2-Thiophene)
				z R = 4-(2-Methylpyrrole)

Scheme 1.

General Heffe synthesis of 1-(4-substitutedphenyl)-2-pyrrolidin-1-yl-pentan-1-ones, **4ab**

^aReagents and conditions: i) *n*-BuMgCl; ii) H₂SO₄; iii) AlCl₃, Br₂; iv) pyrrolidine

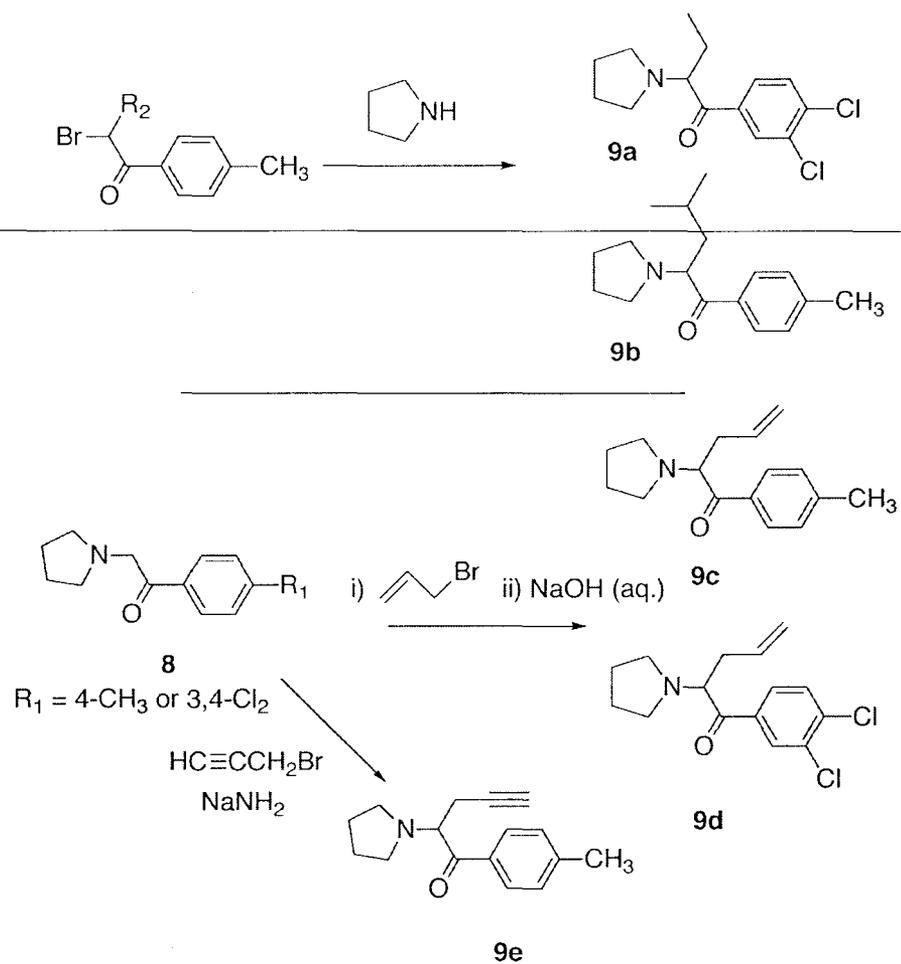
^bThe Heffe synthesis was not followed for certain compounds. Synthetic details for those compounds are presented in the Experimental Section and are discussed in the text.



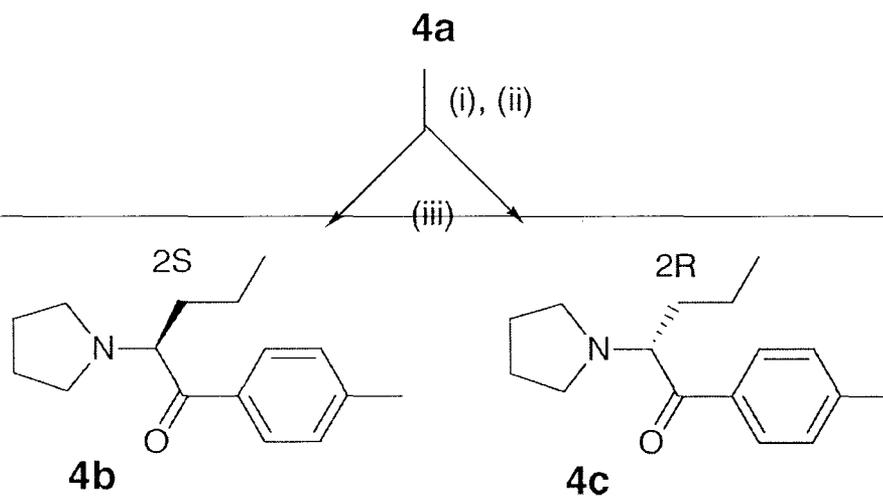
Scheme 2.

Synthesis of Analogs 6, 7, 9f and 9ga

^aReagents and conditions: (i) AlCl₃, Br₂; (ii) Li₂CO₃, LiBr, DMF; (iii) pyrrolidine HCl, (HCHO)_n; (iv) pyrrolidine; (v) *n*-BuNH₂; (vi) piperidine



Scheme 3.
Synthesis of Compounds 9a-e



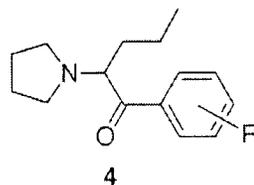
Scheme 4.

Resolution of 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one, **4aa**

^aReagents: (i) Dibenzoyl-D (or L)-tartaric acid, EtOH; (ii) Recrystallization (CH₂Cl₂/hexanes); (iii) Na₂CO₃, Et₂O

Table 1

The affinity of 4 ($[^{125}\text{I}]\text{RTI 55}$) and its inhibition of uptake of $[^3\text{H}]\text{dopamine}$, $[^3\text{H}]\text{serotonin}$, and $[^3\text{H}]\text{norepinephrine}$ by HEK-hDAT, HEK-hSERT and HEK-hNET cells^a



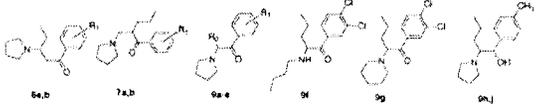
Cpd 4	R	DAT K _i (nM)	DA Uptake (IC ₅₀)	DR ^b	SERT K _i (nM)	SER Uptake (IC ₅₀)	NET K _i (nM)	NE Uptake (IC ₅₀)
	Cocaine	432 ± 29	461 ± 46	1.06	358 ± 24	494 ± 51	2150 ± 190	378 ± 48
a	O-2371 4-CH ₃ (R/S)	21.4 ± 4.6	52.0 ± 20	2.43	3770 ± 560	2780 ± 590	195 ± 26	28.3 ± 8.1
b	O-2442 4-CH ₃ (S)	18.1 ± 3.0	16.3 ± 2.3	0.91	2220 ± 550	1070 ± 230	109 ± 45	11.3 ± 2.4
c	O-2440 4-CH ₃ (R)	1330 ± 300	1790 ± 320	1.35	>10 μM		>10 μM	
d	O-2387 H	33.7 ± 5.4	52.3 ± 6.2	1.55	>10 μM		199 ± 45	56.0 ± 13
e	O-2370 4-F	82.0 ± 25	185 ± 62	2.26	>10 μM		830 ± 140	171 ± 35
f	O-2419 4-Br	51.0 ± 6.7	39.5 ± 7.5	0.77	830 ± 190	1050 ± 90	386 ± 53	83.0 ± 30
g	O-2493 4-I	81.4 ± 9.2	32.0 ± 11	0.39	301 ± 26	197 ± 35	310 ± 34	46.5 ± 8.4
h	O-2495 3-I	109 ± 32	52.0 ± 16	0.48	1400 ± 120	1070 ± 170	670 ± 130	81.0 ± 20
i	O-2575 4-CN	5900 ± 1100	1000 ± 170	0.17	>10 μM		>10 μM	
j	O-2577 4-CH ₂ OH	48.7 ± 2.2	44.3 ± 8.4	0.91	>10 μM		150 ± 23	12.4 ± 2.8
k	O-2418 4-OH	125 ± 23	49.7 ± 3.4	0.40	>10 μM		1290 ± 480	86.7 ± 7.5
l	O-2443 4-NO ₂	266 ± 32	1110 ± 340	4.17	2460 ± 290	1110 ± 450	2690 ± 530	531 ± 67
m	O-2417 4-OCH ₃	329 ± 33	283 ± 66	0.86	4080 ± 410	2430 ± 720	2600 ± 1000	235 ± 8.7
n	O-2558 4-CO ₂ CH ₃	360 ± 140	154 ± 50	0.43	3950 ± 690	2350 ± 560	1140 ± 320	22.8 ± 3.3
o	O-2439 4-NHCOCH ₃	30.2 ± 2.0	67.9 ± 8.4	2.25	>10 μM		4000 ± 1100	317 ± 64
p	O-2481 4-CF ₃	>10 μM			959 ± 92	1030 ± 340	>10 μM	
q	O-2537 4-C≡CCH ₃	61.0 ± 16	11.8 ± 2.8	0.19	6700 ± 1100	3300 ± 1100	69.8 ± 5.4	19.3 ± 4.1
r	O-2479 2-CH ₃	59.7 ± 9.0	63.0 ± 19	1.06	3720 ± 520	2020 ± 670	425 ± 63	19.7 ± 3.3
s	O-2480 3-CH ₃	51.0 ± 14	62.9 ± 6.9	1.23	5900 ± 1600	4400 ± 1100	216 ± 38	9.4 ± 0.8
t	O-2482 Naphthyl	20.1 ± 7.1	40.0 ± 13	1.99	33.1 ± 1.1	46.0 ± 5.5	136 ± 27	11.7 ± 0.9
u	O-2390 3,4-Cl ₂	11.5 ± 1.4	43.0 ± 20	3.91	199 ± 50	600 ± 63	37.8 ± 3.2	21.0 ± 0.6
v	O-2574 3,4-(OH) ₂	84.0 ± 12	42.0 ± 11	0.50	>10 μM		219 ± 71	7.6 ± 2.9
w	O-2512 3,4-(OCH ₃) ₂	>10 μM			7460 ± 770	1540 ± 220	>10 μM	
x	O-2441 4-Furan	105 ± 17	122 ± 18	1.16	3330 ± 1200	2180 ± 440	95 ± 20	93 ± 38
y	O-2438 4-Thiophene	460 ± 120	539 ± 69	1.17	3320 ± 280	1960 ± 720	370 ± 160	263 ± 94
z	O-2446 4-Mepyrole	3850 ± 330	5400 ± 1600	1.40	>10 μM		>10 μM	

^aNumbers represent the means ± SEM from at least three independent experiments, each conducted with duplicate (for binding assays) or triplicate (for uptake assays) determinations. When the K_i or the IC₅₀ for the test compound is greater than 10 μM, only two experiments were conducted and no standard error was reported. Data from Oregon Health & Science University and VA Medical Center, Portland, OR.

^bDR = Discrimination Ratio

Table 2

The affinity of 6, 7 and 9 ($[^{125}\text{I}]\text{RTI 55}$) and their inhibition of uptake of $[^3\text{H}]\text{dopamine}$, $[^3\text{H}]\text{serotonin}$, and $[^3\text{H}]\text{norepinephrine}$ by HEK-hDAT, HEK-hSERT and HEK-hNET cells^a



Cpd		R ₁	R ₂	DAT K _i (nM)	DA Uptake (IC ₅₀)	SERT K _i (nM)	SER Uptake (IC ₅₀)	NET K _i (nM)	NE Uptake (IC ₅₀)
6a	O-2525	4-CH ₃		>10 μM		>10 μM		>10 μM	
6a	O-2524	3,4-Cl ₂		8440 \pm 310	>10 μM	3900 \pm 1000	1780 \pm 220	>10 μM	
7a	O-2477	4-CH ₃		>10 μM		4100 \pm 1800	4800 \pm 1200	>10 μM	
7a	O-2478	3,4-Cl ₂		1530 \pm 520	2900 \pm 1300	630 \pm 110	710 \pm 170	>10 μM	
9a	O-2384	3,4-Cl ₂	CH ₂ CH ₃	28.8 \pm 2.1	55.0 \pm 12	810 \pm 150	441 \pm 12	262 \pm 36	18.5 \pm 8.0
9b	O-2494	4-CH ₃	CH ₂ CH(CH ₃) ₂	13.7 \pm 3.0	5.9 \pm 2.3	2870 \pm 10	2040 \pm 150	259 \pm 80	18.0 \pm 5.0
9c	O-2556	4-CH ₃	CH ₂ CH=CH ₂	90.5 \pm 3.1	55 \pm 17	>10 μM		1400 \pm 370	88.0 \pm 16
9d	O-2557	3,4-Cl ₂	CH ₂ CH=CH ₂	39.9 \pm 5.5	18.3 \pm 3.7	1060 \pm 170	440 \pm 170	509 \pm 100	24.9 \pm 8.2
9e	O-2576	4-CH ₃	CH ₂ C \equiv CH	2310 \pm 110	231 \pm 25	>10 μM		4100 \pm 1300	350 \pm 120
9f	O-2389			520 \pm 110	1190 \pm 58	5080 \pm 60	>10,000	4200 \pm 1200	2520 \pm 190
9g	O-2388			144 \pm 48	666 \pm 89	2460 \pm 260	>10,000	2350 \pm 230	800 \pm 200
9h ^b	O-2529-1			>10 μM		>10 μM		>10 μM	
9j ^b	O-2529-2			>10 μM		>10 μM		>10 μM	

^aNumbers represent the means \pm SEM from at least three independent experiments, each conducted with duplicate (for binding assays) or triplicate (for uptake assays) determinations. When the K_i or the IC₅₀ for the test compound is greater than 10 μM , only two experiments were conducted and no standard error was reported. Data from Oregon Health & Science University and VA Medical Center, Portland, OR.

^bCompounds 9h and 9j are pure diastereomers



New designer drug of abuse: 3,4-Methylenedioxypropylvalerone (MDPV). Findings from apprehended drivers in Finland

Pirkko Kriikku^{a,*}, Lars Wilhelm^b, Olaf Schwarz^b, Janne Rintatalo^c

^a Vita Health Care Services Ltd., Vita Laboratory, Laivakatu 5 F, 00150 Helsinki, Finland

^b LADR GmbH Medizinisches Versorgungszentrum Dr. Kramer und Kollegen, Lauenburger Straße 67, 21502 Geesthacht, Germany

^c National Bureau of Investigation Forensic Laboratory, Jokiniemenkuja 4, 01370 Vantaa, Finland

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ABSTRACT

Starting in 2008 a new designer drug, 3,4-methylenedioxypropylvalerone (MDPV) appeared among users of illegal drugs in Finland. Since then there have been several seizures of MDPV by police and customs and it has been connected to many crimes of different types. In this study the incidence and impact of the use of MDPV in drivers suspected of being under the influence of drugs (DUID) in Finland was assessed.

Since autumn 2009, blood samples from drivers suspected of DUID in Finland have been analysed for the presence of MDPV. A new LC-MS/MS method for the determination of MDPV in serum was established. In order to assess the impact of MDPV on driving performance, drug and alcohol findings of positive MDPV cases were compared with data from the clinical examination carried out while the suspect was under arrest. In a period of one year there were 259 positive MDPV cases from apprehended drivers (5.7% of all confirmed DUID cases). In 80% of the cases in which MDPV was found, amphetamine was also present. Benzodiazepines were also frequently found together with MDPV, which was to be expected since in Finland, in our experience, stimulants are very often used together with benzodiazepines.

In most cases it remained unclear whether the observed psycho-physical achievement deficiency was induced by MDPV because the concentrations of other drugs, especially other stimulants, were often high. However, in some subjects, MDPV, or MDPV in combination with other substances was the most probable cause of the impairment. The concentrations of MDPV varied from 0.016 mg/L to over 8.000 mg/L.

Little is known about the pharmacology of MDPV. However, based on our findings it is clear that MDPV has a serious impact on traffic safety in Finland.

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1. Introduction

MDPV (Fig. 1) is a so-called “designer drug” with stimulant effects similar to cocaine and amphetamine. It is an analogue of propylvalerone, a psychostimulant that was used to treat lethargy and chronic fatigue in the 1970s, but was later withdrawn from the market because of problems with abuse and dependency [1,2]. MDPV structurally resembles cathinone, found in Khat, and has thus been referred to as a synthetic cathinone derivative [3].

MDPV has no medical use and is said to have exceptionally high dependency potential and high risk of psychosis. At higher doses some users report extremely unpleasant “come-down” effects [4]. Police reports indicate that people under the influence of MDPV

very often act violently and unpredictably. MDPV is most often sold as powder, but capsules have also been reported. A wide range of dosage forms and routes of administration are used: oral (capsules or powder dissolved in water), IV, rectal [4].

Very recently, Ojanperä et al. published their results about MDPV findings from the urine of opioid-dependent patients [5], which is, other than our results, the only published study about MDPV in clinical samples. There are, however, some data on the pharmacology and toxicology of other structurally similar designer drugs of pyrrolidinophenone or cathinone types available [6–9]. Also some reports on the structure and determination and *in vitro* metabolism of MDPV have been published recently [10–13].

Since the first seizure of MDPV in Finland in 2008, there have been several deaths where involvement of MDPV was suspected by the police (personal communication). Whether the actual cause of these deaths really was MDPV or perhaps some other drug used in combination with it is still not settled. It seems that MDPV is a major phenomenon only in Finland. There have been some reports

* Corresponding author. Tel.: +358 9 2288 0480; fax: +358 9 2288 0413.

E-mail addresses: pirkko.kriikku@vita.fi, pirkko.kriikku@helsinki.fi (P. Kriikku), wilhelm@ladr.de (L. Wilhelm), janne.rintatalo@poliisi.fi (J. Rintatalo).

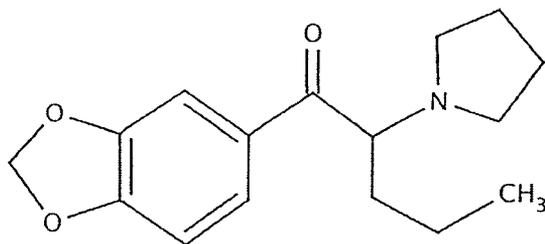


Fig. 1. 1-(3,4-Methylenedioxyphenyl)-2-pyrrolidinylpentan-1-one (methylenedioxypropylvalerone, MDPV).

of cases also in other countries (United Kingdom, Ireland and Sweden) but not on the scale seen in Finland [14–16].

In our laboratory, screening of MDPV was initiated at the request of the Forensic Laboratory of the Finnish National Bureau of Investigation (NBI), after there had been several seizures of MDPV by police. The drug screening procedures currently used by the police in Finland (e.g. DrugWipe, Securetec/Afiniton, William-sport, PA, USA), fail to detect MDPV, as is true for most other designer drugs. Since August 2009 blood samples from drivers suspected of being under the influence of drugs (DUID) have been analysed for the presence of MDPV. Initially, a qualitative screening method using LC–MS/MS was developed. After a commercial reference standard came available, it became possible to convert this assay into the quantitative confirmation method for the determination of MDPV described in this paper.

In many DUID cases in Finland the suspect is given a psycho-physical achievement test by a physician after the arrest. The requirement for the test is determined by the severity of the suspected crime. The test includes specific psychomotor and cognitive tasks and questions. Based on the results of the tests the physician describes the overall functional impairment of the subject using a three-step scale: within the normal range, mild aberrations, moderate or greater aberrations. Although such tests provide evidence of drug effects on the arrested driver, they do not specifically demonstrate driving impairment [17]. Furthermore, due to the possible impact of acute and chronic tolerance, blood concentrations do not necessarily reflect the degree of impairment observed in the psycho-physical achievement test. These issues lead to difficulty in establishing guidelines for the concentrations of drugs that are dangerous or impair driving. In Finland, the authorities do not need to prove actual driving impairment when a suspect of DUID is taken into custody; a suspicion of DUID is a sufficient reason for the arrest. The psycho-physical achievement deficiency test provides additional information that can be used in setting penalties: higher penalties in cases with aberrations.

The aim of this study was to report on the prevalence and significance of MDPV among drivers apprehended for DUID in Finland. In MDPV positive cases, drug and alcohol findings were compared with data from the clinical examination carried out while the suspect was under arrest. The psycho-physical achievement deficiency information was used to evaluate the significance of the presence of MDPV in DUID cases. We also report concentrations of MDPV in the blood of DUID offenders.

2. Materials and methods

2.1. Chemicals and reagents

The reference standard of MDPV (purity 98%) used for the quantitative determination and the (±)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5) used as internal standard were obtained from LGC Standards (Wesel, Germany). For the qualitative analysis that was used before the availability of a reference standard made a quantitative assay possible, a seized MDPV sample (VARA-4108, purity 4%) supplied by NBI Forensic Laboratory, Vantaa, Finland was used to develop the assay and check reproducibility. HPLC grade methanol, water, ammonia 32% p.a. and acetic acid p.a.

were purchased from Baker (Griesheim, Germany) and formic acid 98–100% from Merck (Darmstadt, Germany). As the solid phase column an OASIS HLB 1 cc 30 mg from Waters (Eschborn, Germany) was used.

2.2. Sample preparation

The first step of sample preparation consisted of adding 0.8 mL 0.1 M acetic acid and 20 μ L of an internal standard solution to 0.2 mL of test material (serum or control). The internal standard solution contained 500 ng/mL MDEA-d5 in methanol. Spiked samples were vortex mixed for 10 s and centrifuged at 13 000 rpm for 3 min.

Sample cleanup was performed by solid phase extraction (SPE) using OASIS HLB cartridges with 30 mg sorbent. The SPE cartridges were conditioned with 1 mL of methanol and 1 mL of deionised water. Supernatants were loaded on the cartridges and drawn through under gravity flow. The cartridges were washed with 1 mL of a mixture of deionised water, methanol and ammonia (93:5:2, v/v/v) and 1 mL of a mixture of deionised water, methanol and ammonia (78:20:2, v/v/v). The cartridges were dried for 10 min in order to remove washing solutions. The analytes were then desorbed with 1 mL methanol and acetic acid (95:5, v/v). The eluted solutions were evaporated under a nitrogen stream at 45 °C, and the residue was reconstituted with 0.5 mL of a mixture of methanol and 10 mM NH_4 acetate in 0.1% formic acid (80:20, v/v). After vortex mixing, 5 μ L sample was injected into the LC–MS/MS system.

2.3. LC–MS/MS conditions

The LC–MS/MS system consisted of a Shimadzu LC 20A LC-system and a triple quadrupole mass spectrometer (API 4000, SCIEX) with Turbo Ion Spray. Chromatography with a total runtime of 5.5 min was performed using a phenyl-hexyl 50 mm \times 3.0 mm 3 μ m column from Phenomenex operated in gradient mode at 0.5 mL/min. Solvent A consisted of methanol and Solvent B of 10 mM NH_4 acetate in 0.1% formic acid. The column oven temperature was set to 40 °C. Multiple reaction monitoring (MRM) was created for the analyte and internal standard (MDPV m/z 276/126 and m/z 276/135, MDEA-d5 m/z 213/163) in positive ion mode at the ionisation voltage of 4200 V, the source temperature being 550 °C.

Integration of peak areas and standard calibration for the MRM transitions were performed using the quantification tool of Analyst 1.5.1 software (SCIEX). Confirmatory analysis was performed based on the ratio of two MRM transitions detected for each analyte.

The validation of the method was performed according to the guidelines of the CTfCh (Gesellschaft für Toxikologie und Forensische Chemie) for limit of detection, limit of quantification, precision, recovery, selectivity and matrix effect [18]. No interference was found with any of the 38 most commonly occurring stimulants, sedatives and opioids that were analysed together with MDPV. The procedure also included verification of isobar mass transitions from the literature [19,20]. The calculations for the limit of detection were performed according to the German standard specification DIN 32645 [21].

The limit of detection (LOD) for MDPV was 0.003 mg/L and the limit of quantification 0.011 mg/L. The calibration was linear over the range 0.010–0.500 mg/L. For sample concentrations exceeding the calibration range the curve was extended and an approximate value was given as a result. The extraction recovery was determined at the lowest and highest point of the calibration in blank serum, and was found to be 67.9% at 0.200 mg/L and 89.8% at 0.020 mg/L. The matrix effect, measured in 6 different samples, was 21.5%. Precision was measured at two different concentrations, 0.015 mg/L and 0.400 mg/L, by performing two analyses on 8 different days. The standard deviation (CV) of within- and between-day repeatability was between 9.5% and 11.8%. Accuracy ranged between 3.9% and 5.2%.

LC–MS/MS chromatograms of a blank, a spiked sample and a real sample are presented in Figs. 2–4.

3. Results and discussion

Prior to development of the quantitative assay, the screening assay was used to determine whether samples were positive or negative for the presence of MDPV, i.e., above or below the limit of detection for MDPV, 0.003 mg/L. After the quantitative assay became available, samples were initially screened using the non-quantitative assay and for those found to be positive the quantitative assay was performed using a separate aliquot of serum.

In Finland, the number of cases per year of driving under the influence of drugs or alcohol in which a blood sample is taken is over 12 500. In approximately 4570 of them a drug analysis was requested. MDPV is, however, not screened from every sample. Between 28 August 2009 and the end of August 2010, blood

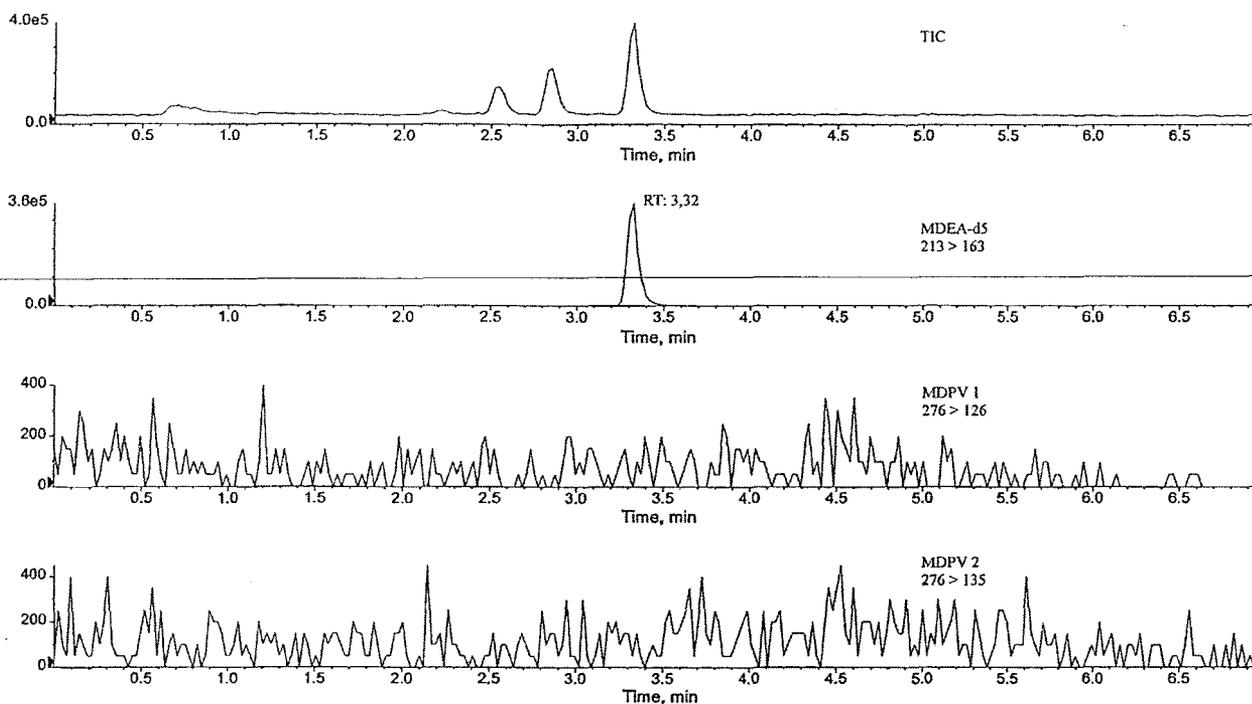


Fig. 2. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a blank sample with 0.050 mg/L of internal standard (\pm)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

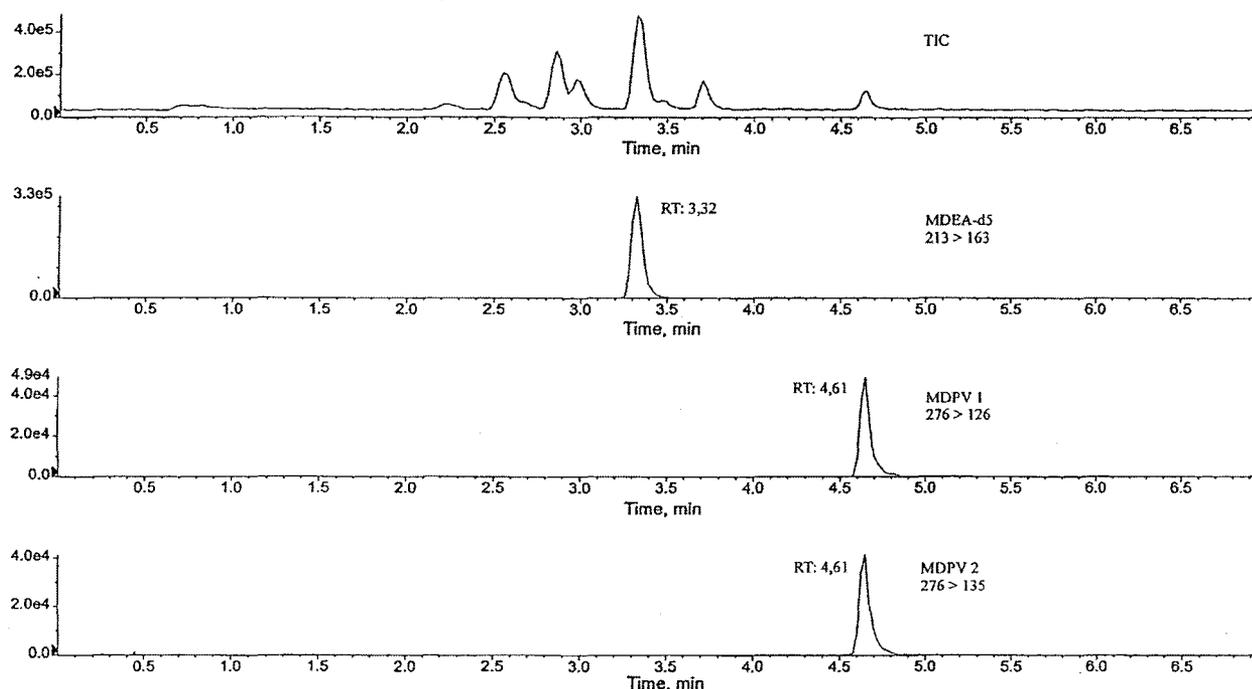


Fig. 3. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a blank sample spiked with a concentration of 0.015 mg/L of methylenedioxypropylvalerone (MDPV) and with 0.050 mg/L of internal standard (\pm)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

samples from about 3000 drivers apprehended on suspicion of DUID were analysed for the presence of MDPV. These cases were not selected randomly and are not necessarily representative of the overall DUID population. They were selected partly on the basis of the needs of and information provided by the police, e.g., drivers admitted use of MDPV or amphetamine-like drugs, failure to detect other drugs which could explain aberrant behaviour. A positive

immunological blood screening test for amphetamines was also an indication for an MDPV analysis, even though MDPV does not show in that test.

Of the samples screened for MDPV in this one year period, 259 (8.6%, $n = 3000$) were found to be positive. This represents approximately 5.7% of all confirmed DUID cases excluding alcohol-only cases ($n = 4570$) in Finland over the same time

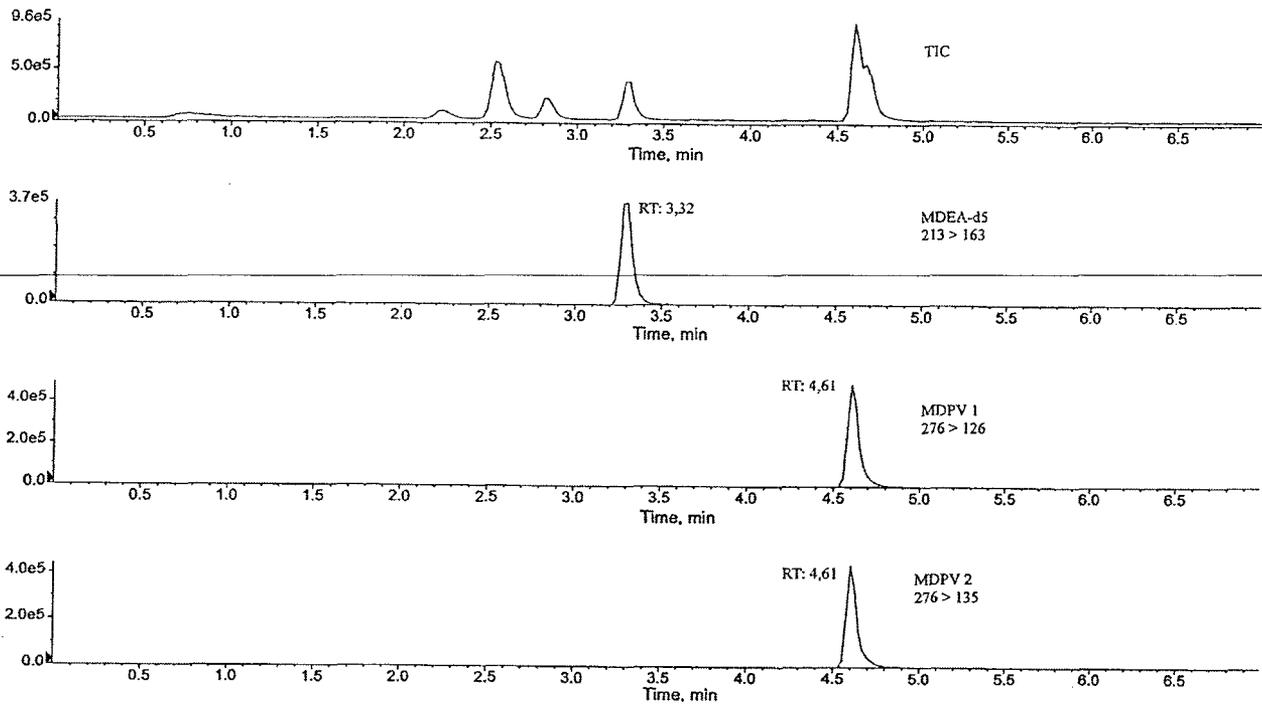


Fig. 4. Total ion chromatogram (TIC) and extracted ion chromatograms (XTC) of a representative positive sample from an apprehended driver containing 0.164 mg/L of methylenedioxypropylvalerone (MDPV) and 0.050 mg/L of internal standard (\pm)-3,4-methylenedioxyethylamphetamine-d5 (MDEA-d5).

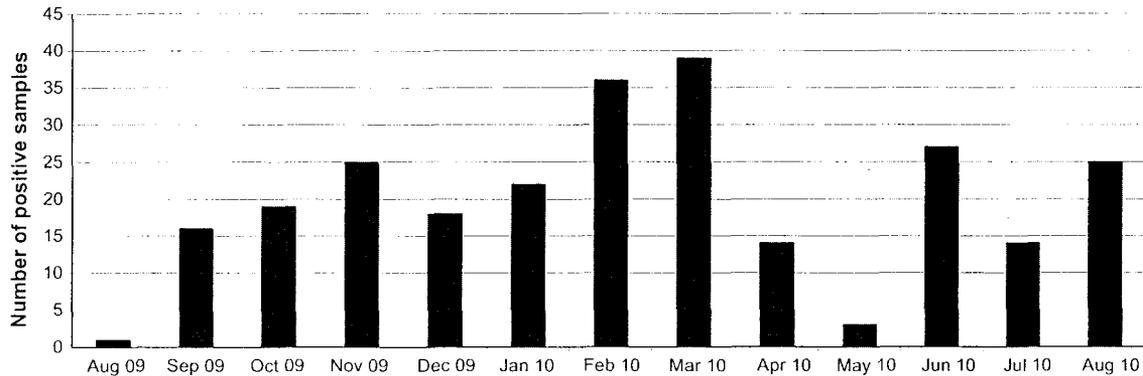


Fig. 5. The numbers of positive methylenedioxypropylvalerone (MDPV) samples among apprehended drivers in Finland between 28 August 2009 and the end of August 2010.

period. The monthly numbers of positive MDPV samples between August 2009 and August 2010 are illustrated in Fig. 5. 87% of the MDPV positive drivers were male, 96% were from Southern Finland and 76% were between 25 and 44 years.

Of all the 259 MDPV positive cases, in 80% amphetamine and in 67% benzodiazepines were also present. A combination of MDPV, amphetamine and benzodiazepines was found in 54% of the cases. Interestingly, MDPV was often found together with phenazepam, which is a widely abused benzodiazepine that has not been approved for prescription use in Finland. Alcohol was present in only 22 cases (8.5%) and in 18 of them was below the level (0.5 g/L) that defines intoxication in Finland. Surprisingly, the levels of benzodiazepines and most other drugs were often low compared to levels associated with major behaviour effects. However, the levels of other stimulants found together with MDPV were in most cases high. The high percentage of multi-drug findings among the positive MDPV samples is generally typical of DUID cases in Finland [22]. In 8 cases were no other compounds besides MDPV found.

The concentrations of MDPV in samples from a typical month, August 2010, are shown in Fig. 6. The concentration range is very

similar to the range of amphetamine concentrations that we see in the DUID samples in Finland. There were two remarkable outliers (2.4 mg/L and 8.4 mg/L) in these samples. Unfortunately, no data

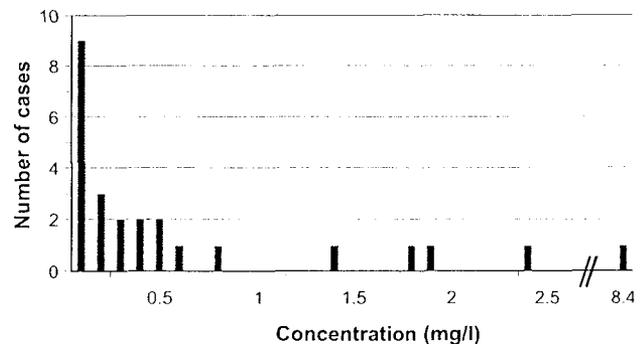


Fig. 6. Concentrations of methylenedioxypropylvalerone (MDPV) found in the 25 blood samples from apprehended drivers selected for analysis in August 2010.

Table 1
Concentrations of methylenedioxypropylvalerone (MDPV) and other drugs in positive samples from August 2010.

Sample	MDPV (mg/L)	Benzodiazepines ^a	Stimulants ^b	Cannabis ^c	Other findings	Clinical examination
1-08/2010	0.430	±	++		Ethanol	Normal
2-08/2010	1.700	±	++			Aberrations monitored, no overall functional disorder
3-08/2010	1.310	+	++			Aberrations and functional disorder monitored
4-08/2010	2.400					
5-08/2010	0.049	±	++			Aberrations monitored, no overall functional disorder
6-08/2010	0.330	++	++		Methadone	Aberrations and functional disorder monitored
7-08/2010	0.020		++	+		Aberrations and functional disorder monitored
8-08/2010	0.142		+			
9-08/2010	0.020	±	++			
10-08/2010	0.860	±	++	±		Normal
11-08/2010	0.270	+	+		Methadone	Aberrations monitored, no overall functional disorder
12-08/2010	0.050		++			
13-08/2010	0.031	+	++		Zolpidem	
14-08/2010	0.020	±	+		Buprenorphine, tramadol	Aberrations monitored, no overall functional disorder
15-08/2010	0.090		++		Methylphenidate	
16-08/2010	0.380	±	+			Aberrations and functional disorder monitored
17-08/2010	0.550	+	+			
18-08/2010	8.400		++		Methadone	
19-08/2010	0.120	+	++			Aberrations monitored, no overall functional disorder
20-08/2010	0.450	+	++			Aberrations monitored, no overall functional disorder
21-08/2010	0.240	+	++	±		Aberrations and functional disorder monitored
22-08/2010	0.044		++			Normal
23-08/2010	0.044	+	++			
24-08/2010	1.900	±	+			Normal
25-08/2010	0.110		+	+		

- ^a ±One or more benzodiazepines with insignificant concentrations.
+One or more benzodiazepines at concentrations up to those seen at prescribed doses.
++One or more benzodiazepines with concentration above those seen at prescribed doses.
^b +Amphetamine, methamphetamine or MDMA concentration <0.100 mg/L.
++Amphetamine, methamphetamine or MDMA concentration ≥0.100 mg/L.
^c ±No THC, but THC-COOH positive.
+THC positive.

either on history of drug use or clinical examinations are available in these two cases.

The psycho-physical achievement deficiency test was performed on 208 MDPV positive cases. Functional impairment was found in 84% of these 208 cases but in only 7% was the impairment rated as moderate or greater. Typically the observed aberrations included difficulty in defining the current time, walking in a straight line, turning around and speech. As already mentioned, this evaluation does not demonstrate driving impairment directly, but does give some insight into the impact the drugs had on the subject at the time of the examination. In particular, the impaired judgement and increased willingness to take risks that are associated with the use of stimulants do not necessarily show in the clinical examination.

A summary of the levels of MDPV and other drugs and findings in the clinical tests of the 25 positive samples from August 2010 is illustrated in Table 1. In most MDPV positive cases there was also a considerable amount of amphetamine present in the blood of the suspect. However, there have been some cases where there was reason to believe that the impairment was mainly caused by MDPV. Overall, in 60 of the 259 MDPV positive cases, the analyses showed no other substances, or, the substances found were not at levels sufficient to explain the driving impairment that lead to the arrest. In most of such cases no clinical examination was performed. We introduce one case as an example, where the clinical examination was indeed performed and the concentrations of other drugs beside MDPV were relatively low (case 16-08/2010 in Table 1). The samples of this case were received from the police in Helsinki in the middle of August 2010. The suspected DUI offender was a 28-year old male who had been driving a van at night and had been reported to the police by a citizen. The reason for the report is not known. A roadside drug test was performed on the suspect and it showed positive results for benzodiazepines and amphetamines. The suspect showed aberrations in the clinical

examination, including: unstable gait, balance problems in Romberg's test, his thinking was not clear, depressed and apathetic mood and pupil reaction to light was delayed. In the opinion of the examining physician, the suspect also attempted to disguise his impairment in order to give a misleading impression of normal functioning. The overall functional impairment was, however, estimated to be moderate. The drug analysis of the suspect's blood showed 0.380 mg/L MDPV, low concentrations of benzodiazepines (alprazolam 0.002 mg/L, nordiazepam 0.020 mg/L and oxazepam 0.094 mg/L) and relatively low concentrations of other stimulants (amphetamine 0.092 mg/L and methamphetamine 0.023 mg/L). These other findings were considered to be insignificant in respect to the suspected driving impairment.

There were 219 seizures of MDPV by Finnish Police between 1 January and 31 June 2010 (Fig. 7), accounting for about 45% of all designer drug seizures. Samples of the seized materials were analysed in NBI Forensic Laboratory, Vantaa, Finland. Some samples were found to contain MDPV alone but others contained various mixtures which combined MDPV with benzodiazepines (especially phenazepam) and with other stimulants (especially amphetamine). MDPV confiscated by the Finnish customs has been of Chinese origin.

In the view of the fact that in the past 10 years over 100 new psychotropic substances have appeared on the illicit drug market all over the world, the incidence of MDPV among drivers in Finland is exceptional [23]. MDPV was first reported as new psychoactive substance to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol in 2009 [24]. In Finland MDPV was classified as an illegal drug in June 2010. It has been shown that law enforcement is not a particularly effective deterrent and does not necessarily decrease the prevalence of a particular drug among drivers [25]. However, prior to June 2010 MDPV distributors had the advantage that the drug was not illegal. Presumably, its new designation as an illegal drug will make it less

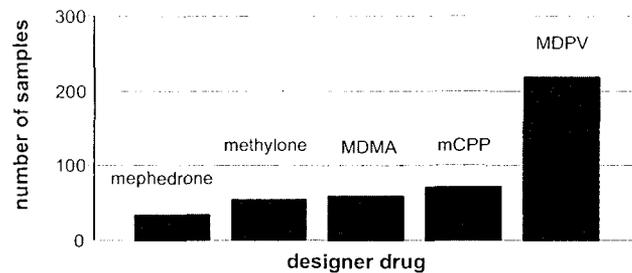


Fig. 7. Most abundant designer drugs seized in Finland between 1 January and 31 August 2010 and analysed by the Finnish National Bureau of Investigation Forensic Laboratory, Vantaa, Finland.

attractive to distributors and result in reduced availability of MDPV.

4. Conclusions

Given the non-random sample selection process and the fact that clinical evaluation and quantitative MDPV data was only available for a sub-set of the samples, the results must be interpreted with particular caution. Nevertheless, it can be concluded that the incidence of MDPV in confirmed DUID cases (excluding alcohol-only cases) is at least 5.7% and could be higher. This is a remarkable number considering that MDPV is a relatively new substance that has only been in Finland for about 2 years. The preponderance of males among MDPV positive cases is typical of all kinds of DUID cases and the 25–44 age range is typical of non-alcohol DUID cases, in our experience. The very high percentage of MDPV positive cases from Southern Finland is somewhat unusual and may reflect a limited distribution of the drug in Finland at this time. The data strongly suggest that MDPV is responsible for at least a portion of the behavioural abnormalities and driving difficulties observed. Since MDPV is most often found together with other psychoactive drugs, it is difficult to determine whether the observed driving impairment was indeed caused by MDPV exclusively, or rather by the combined effect of several substances. However, the results of this study show that MDPV use is a significant problem in DUID cases in Finland. Since at this point it has only been a few months since the legislative change in respect to MDPV, more time is needed to determine whether a decline in the incidence of the drug among Finnish drivers will be achieved. In addition, further studies are needed in order to gain more information on the pharmacology and toxicology of MDPV and to be able to determine what concentrations are dangerous.

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References

- [1] G. Gardos, J.O. Cole, Evaluation of pyrovalerone in chronically fatigued volunteers, *Curr. Ther. Res.* 13 (1971) 631–635.
- [2] P. Deniker, H. Loo, H. Cuche, J.M. Roux, Abuse of pyrovalerone by drug addicts, *Ann. Med. Psychol.* 2 (1975) 745.
- [3] S. Gibbons, M. Zloh, An analysis of the 'legal high' mephedrone, *Bioorg. Med. Chem. Lett.* 20 (2010) 4135–4139.
- [4] Psychonaut WebMapping Research Group, MDPV Report, Institute of Psychiatry, King's College London, London, UK, 2009.
- [5] I.A. Ojanperä, P.K. Heikman, I.J. Rasanen, Urine analysis of 3,4-methylenedioxy-pyvalerone in opioid-dependent patients by gas chromatography–mass spectrometry, *Ther. Drug Monit.* (2011), doi:10.1097/FTD.0b013e318208b693.
- [6] C. Sauer, F.T. Peters, C. Haas, M.R. Meyer, G. Fritschi, H. Maurer, New designer drug α -pyrrolidinovalerophenone (PVP): studies on its metabolism and toxicological detection in rat urine using gas chromatographic/mass spectrometric techniques, *J. Mass Spectrom.* 44 (2009) 952–964.
- [7] H.H. Maurer, T. Kraemer, D. Springer, R.F. Staack, Chemistry, pharmacology, toxicology and hepatic metabolism of designer drugs of the amphetamine (ecstasy), piperazine, and pyrrolidinophenone types, *Ther. Drug Monit.* 26 (2004) 127–131.
- [8] S.D. Brandt, R.C.R. Wootton, G. De Paoli, S. Freeman, The naphyrone story: the alpha or beta-naphthyl isomer? *Drug Test. Anal.* (2010), doi:10.1002/dta.185.
- [9] F. Schifano, A. Albanese, S. Fergus, J.L. Stair, P. Deluca, O. Corazza, Z. Davey, J. Corkery, H. Siemann, N. Scherbaum, M. Farre, M. Torrens, Z. Demetrovics, A.H. Ghodse, Psychonaut Web Mapping, RedNet Research Group, Mephedrone (4-methylcathinone; 'meow meow'): chemical, pharmacological and clinical issues, *Psychopharmacology*, doi:10.1007/s00213.010.2070.x.
- [10] J.C. Yohannan, J.S. Bozenko Jr., The characterization of 3,4-methylenedioxy-pyvalerone (MDPV), *Microgram J.* 7 (2010) 12–15.
- [11] F. Westphal, T. Junge, P. Rösner, F. Sönnichsen, F. Schuster, Mass and NMR spectroscopic characterization of 3,4-methylenedioxy-pyvalerone: a designer drug with α -pyrrolidinophenone structure, *Forensic Sci. Int.* 190 (2009) 1–8.
- [12] M.R. Meyer, P. Du, F. Schuster, H.H. Maurer, Studies on the metabolism of the α -pyrrolidinophenone designer drug methylenedioxy-pyrovalerone (MDPV) in rat and human urine and human liver microsomes using GC–MS and LC–high-resolution MS and its detectability in urine by GC–MS, *J. Mass Spectrom.* 45 (2010) 1426–1442.
- [13] S. Strano-Rossi, A.B. Cadwallader, X. de la Torre, F. Botrè, Toxicological determination and *in vitro* metabolism of the new designer drug methylenedioxy-pyvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry, *Rapid Commun. Mass Spectrom.* 24 (2010) 2706–2714.
- [14] Europol–EMCDDA Joint Report on a New Psychoactive Substance: 4-Methylmeth-cathinone (Mephedrone).
- [15] S. Fröblich, E. Lambe, J. O'Dea, Acute liver failure following recreational use of psychotropic "head shop" compounds, *Ir. J. Med. Sci.*, doi:10.1007/s11845.010.0636.6.
- [16] Elva åtalas i stor knarkhärva, Svenska Dagbladet, 22 October 2010, http://www.svd.se/nyheter/inrikes/elva-atalas-i-stor-knarkharva_5549347.svd (accessed 23.11.2010).
- [17] A.W. Jones, Age- and gender-related differences in blood amphetamine concentrations in apprehended drivers: lack of association with clinical evidence of impairment, *Addiction* 102 (2007) 1085–1091.
- [18] Richtlinien der GTFCh zur Qualitätssicherung forensisch-toxikogischer Untersuchungen vom 01.06.2009.
- [19] B. Güssregen, S. Schröfel, M. Nauck, T. Arndt, Selective Reaction Monitoring (SRM) Daten von mehr als 900 Xenobiotika für Aufbau und Validierung von LC–MS/MS Analysen, *Toxichem Krimtech* 75 (3) (2008) 149–174.
- [20] S. Schröfel, B. Güssregen, A. Werle, M. Nauck, T. Arndt, Selective Reaction Monitoring (SRM) Daten von Xenobiotika für Aufbau und Validierung von LC–MS/MS Analysen – Teil 2, *Toxichem Krimtech* 77 (2) (2010) 117–136.
- [21] DIN EN ISO/IEC 32645, 1994.
- [22] K.K. Karjalainen, T.P. Lintonen, A.O. Impinen, P.M. Lillsunde, A.I. Ostamo, Poly-drug findings in drugged driving cases during 1977–2007, *J. Subst. Abuse* 15 (2010) 143–156.
- [23] A. Wohlfarth, W. Weinmann, Bioanalysis of new designer drugs, *Bioanalysis* 2 (2010) 965–979.
- [24] EMCDDA–Europol 2009 Annual Report on the Implementation of Council Decision 2005/387/JHA.
- [25] A.W. Jones, A. Holmgren, F.C. Kugelberg, Driving under the influence of central stimulant amines: age and gender differences in concentrations of amphetamine, methamphetamine and ecstasy in blood, *Traffic Inj. Prev.* 6 (2005) 317–322.

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Recreational Water Illness and Injury Prevention Week — May 23–29, 2011

May 23–29, 2011, marks the seventh annual Recreational Water Illness and Injury Prevention Week. This observance highlights simple steps swimmers and pool operators can take to reduce health and safety risks at pools, water parks, and other recreational water venues.

Recreational water illness can result from ingesting, inhaling aerosols of, or having contact with contaminated water in swimming pools, hot tubs, water parks, water play areas, interactive fountains, lakes, rivers, or oceans. These illnesses also can be caused by chemicals in the water or chemicals that evaporate from the water.

This year's observance focuses on preventing swimmer's ear (acute otitis externa), a common and painful infection of the outer ear canal that results in 2.4 million health-care visits and nearly half a billion dollars in health-care costs every year (1). Simple steps, such as keeping ears as dry as possible, can help prevent this illness. More information on preventing swimmer's ear is available at <http://www.cdc.gov/healthywater/swimming/rwi/illnesses/swimmers-ear-prevention-guidelines.html>.

Injuries and drowning also can occur in and around the water. Drowning is the second leading cause of unintentional injury death among children aged ≤ 14 years (2). Additional information on drowning prevention is available at <http://www.cdc.gov/safekid/drowning/index.html>.

References

1. CDC. Estimated burden of acute otitis externa—United States, 2003–2007. *MMWR* 2011;60:605–9.
2. CDC. Web-based Injury Statistics Query and Reporting System (WISQARS). Available at <http://www.cdc.gov/injury/wisqars>. Accessed April 29, 2011.

Estimated Burden of Acute Otitis Externa — United States, 2003–2007

Acute otitis externa (AOE) (swimmer's ear) is inflammation of the external auditory canal most often caused by bacterial infection. AOE is characterized by pain, tenderness, redness, and swelling of the external ear canal, and occasionally, purulent exudate. AOE is associated with water exposure (e.g., recreational water activities, bathing, and excessive sweating) and warm, humid environments (1–5). Because the overall burden and epidemiology of AOE in the United States have not been well described, data from national ambulatory-care and emergency department (ED) databases were analyzed to characterize the incidence, demographics, and seasonality of AOE and associated health-care costs. The analysis showed that in 2007, an estimated 2.4 million U.S. health-care visits (8.1 visits per 1,000 population) resulted in a diagnosis of AOE. Estimated annual rates of ambulatory-care visits for AOE during 2003–2007 were highest among children aged 5–9 years (18.6) and 10–14 years (15.8); however, 53% of visits occurred among adults aged ≥ 20 years (5.3). Incidence peaked during summer months, and the regional rate was highest in the

INSIDE

- 610 Reasons for Not Seeking Eye Care Among Adults Aged ≥ 40 Years with Moderate-to-Severe Visual Impairment — 21 States, 2006–2009
- 614 Arthritis as a Potential Barrier to Physical Activity Among Adults with Obesity — United States, 2007 and 2009
- 619 Ten Great Public Health Achievements — United States, 2001–2010
- 624 Emergency Department Visits After Use of a Drug Sold as "Bath Salts" — Michigan, November 13, 2010–March 31, 2011
- 628 Notes from the Field: Update on Human *Salmonella* Typhimurium Infections Associated with Aquatic Frogs — United States, 2009–2011
- 629 Announcements



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South (9.1). Direct health-care costs for nonhospitalized AOE visits total as much as \$0.5 billion annually, and ambulatory-care clinicians spend nearly 600,000 hours annually treating AOE. Suggested AOE prevention measures include reducing exposure of the ears to water (e.g., using ear plugs or swim caps and using alcohol-based ear-drying solutions) (3–5). To reduce the national incidence of AOE, additional preventive measures should be investigated, and effective prevention messages should be developed and disseminated.

To help direct future prevention efforts for AOE, the current epidemiology of AOE in the United States and its impact on the U.S. health-care system must be understood and quantified. Ambulatory-care estimates were calculated by using 2003–2007 National Ambulatory Medical Care Survey (NAMCS) data,* and ED estimates by using 2007 Nationwide Emergency Department Sample (NEDS) data.† Total national visits were estimated by summing the NAMCS and NEDS estimates, and a range derived by summing the respective 95% confidence limits.§

The 2006–2007 Marketscan database¶ was used to estimate costs for nonhospitalized visits (ambulatory-care visits and ED visits that did not result in hospital admission). Only visits resulting in a diagnosis of AOE without concurrent otitis media were included in the analyses.** Statistical software was used to apply sampling weights and account for complex sample design. Statistical significance was determined by the Rao-Scott modified chi-square test (alpha = 0.05).

AOE was diagnosed in an estimated 2,067,335 ambulatory-care clinic visits and 377,440 ED visits (Table) during 2007, for a total of 2,444,775 (range: 1,953,159–2,936,392) visits for AOE, representing 8.1 visits per 1,000 population (range: 6.5–9.7).†† Thus, an estimated one in 123 persons was affected by AOE in the United States during 2007. AOE accounted for an estimated one in 324 ED visits and one in 481 ambulatory-care visits.

* A national sample of visits to nonfederally employed, office-based physicians from CDC's National Center for Health Statistics.

† A national sample of hospital-based ED visits from the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality.

§ Range is derived by summing respective 95% confidence limit upper and lower bounds, but does not represent a 95% confidence limit for the summary estimate.

¶ The Marketscan Commercial Claims and Encounters database, from Thomson Reuters, includes insurance claims and payments for commercially insured patients only, unlike the other databases used in this analysis, which include data on patients with all types of insurance and the uninsured. Costs (the sum of insurer and out-of-pocket payments, including prescription drug costs) are in 2007 dollars.

** AOE includes *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 380.10, 380.12, and 380.14; otitis media includes codes 381.0–382.9. Concurrent otitis media was diagnosed in 16.5% of total ambulatory-care AOE visits before exclusion.

†† Based on U.S. Census Bureau population data. Available at <http://www.census.gov/popest/estimates.html>.

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TABLE. Estimated number of ambulatory-care and emergency department visits with a recorded diagnosis of acute otitis externa, by selected characteristics — United States, 2003–2007*

Characteristic	Ambulatory				Emergency department†			
	No. (1,000s) [§]	(%)	95% CI (1,000s)	Rate (per 1,000) [¶]	No. (1,000s) [§]	(%)	95% CI (1,000s)	Rate (per 1,000) [¶]
Year								
2003	2,686	—	(1,772–3,560)	9.3	—	—	—	—
2004	2,460	—	(1,898–3,022)	8.4	—	—	—	—
2005	1,884	—	(1,264–2,504)	6.4	—	—	—	—
2006	1,728	—	(1,153–2,303)	5.8	—	—	—	—
2007	2,067	—	(1,597–2,537)	6.9	377	—	(356–399)	1.3
Age (yrs)								
0–4	142**	7	(70–213)	6.9	30	8	(28–33)	1.5
5–9	367	17	(196–538)	18.6	41	11	(38–44)	2.0
10–14	328	15	(223–434)	15.8	41	11	(38–44)	2.0
15–19	186	9	(124–247)	8.8	32	8	(30–34)	1.5
20–39	283	13	(177–389)	3.5	135	36	(127–142)	1.6
40–64	613	28	(437–789)	6.4	82	22	(76–88)	0.8
≥65	247	11	(183–311)	6.7	17	5	(15–19)	0.4
Sex								
Female	1,159	54	(928–1,391)	7.7	208	55	(196–219)	1.4
Male	1,006	46	(823–1,188)	6.9	169	45	(159–180)	1.1
Region††								
Northeast	434	20	(331–537)	7.9	68	18	(56–80)	1.2
Midwest	463	21	(314–613)	7.0	83	22	(73–92)	1.2
South	976	45	(757–1,196)	9.1	158	42	(145–171)	1.4
West	291	14	(238–345)	4.3	69	18	(61–76)	1.0
MSA								
Urban	1,806	83	(1,501–2,112)	7.3	291	77	(272–310)	1.2
Rural	359	17	(171–546)	7.3	83	22	(76–89)	1.7

Abbreviations: CI = confidence interval; MSA = Metropolitan Statistical Area.

* Excludes visits for otitis externa with a concurrent diagnosis of otitis media.

† Emergency department data for 2007 only.

§ Annual weighted estimate.

¶ Based on U.S. Census Bureau estimated civilian noninstitutionalized population as of July 1 for each year. Available at <http://www.census.gov/popest/estimates.html>.

** Small sample number might result in unreliable weighted population estimate for this stratum.

†† Geographic regions as defined by the U.S. Census Bureau. Available at <http://www.census.gov/popest/geographic>.

During 2003–2007, annual estimates of ambulatory care visits for AOE varied from 1,728,824 to 2,685,861, with no significant difference by year ($p=0.19$). Children aged 5–9 and 10–14 years had the highest annual visit rates for AOE (Table); however, 52.8% of visits occurred among adults aged ≥ 20 years. Women accounted for 54% of AOE visits, which was not significantly more than for men ($p=0.30$). A similar demographic distribution was observed among ED visits, with the exception that a larger proportion of AOE visits to the ED occurred among persons aged 20–39 years.

Ambulatory-care diagnoses of AOE displayed a pronounced seasonality (Figure); visits peaked in the summer (44% occurred during June–August) and reached their lowest point in the winter. Although ED rates were similar by U.S. region, the annual rate of ambulatory-care visits for AOE was highest in the South (9.1 per 1,000 population) and lowest in the West (4.3) (Table). Urban and rural rates did not differ. An annual mean of 77,077 (3.6%) ambulatory-care visits for AOE

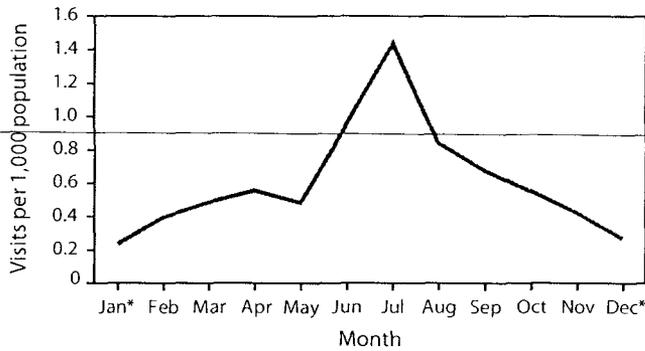
What is already known on this topic?
 Acute otitis externa (AOE) (swimmer's ear) is more likely to occur among swimmers, particularly in warm, humid environments. Greater time spent in the water and greater frequency of head submersion increases the risk for AOE.

What is added by this report?
 This is the first report to describe overall U.S. epidemiology and associated costs of AOE. An estimated 2.4 million U.S. health-care visits result in a diagnosis of AOE annually (8.1 visits per 1,000 population), costing approximately \$0.5 billion in direct health-care costs and nearly 600,000 hours of clinicians' time.

What are the implications for public health practice?
 Although AOE is generally a mild illness, it is a frequently diagnosed condition responsible for a substantial health-care burden. Disseminating effective prevention messages to clinicians and the public could reduce the national impact of AOE.

Morbidity and Mortality Weekly Report

FIGURE. Estimated number of ambulatory-care visits for acute otitis externa per 1,000 population, by month — United States, 2003–2007



* Small sample number might result in unreliable weighted estimates for January and December.

resulted in referral to another physician, but no ambulatory-care AOE patients in the sample were admitted to a hospital. An estimated 2.7% of ED visits for AOE during 2007 led to hospital admission. An estimated 597,761 hours were spent annually by health-care providers on ambulatory-care visits for AOE (median: 15 minutes per visit; mean: 17 minutes). With a mean cost of \$200 per nonhospitalized AOE visit, estimated annual direct health-care payments totaled \$489 million.

Reported by

Emily W. Piercefield, MD, DVM, Div of Applied Sciences, Scientific Education and Professional Development Program Office; Sarah A. Collier, MPH, Michele C. Hlavska, MPH, Michael J. Beach, PhD, Div of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC. **Corresponding contributor:** Emily W. Piercefield, CDC, healthywater@cdc.gov.

Editorial Note

This is the first study to describe the epidemiology of AOE alone (excluding concurrent otitis media) in the general U.S. population and to estimate AOE-associated health-care costs. Exclusion of concurrent otitis media provides a conservative estimate for the actual burden of AOE. The finding of 2.4 million annual visits (8.1 visits per 1,000 population) is consistent with previous reports. As expected, general population rate estimates are slightly lower than in previous reports limited to children aged <18 years (9.9–13.9 per 1,000 population) (6) or when concurrent otitis media was not excluded (3.3 million U.S. outpatient visits) (7).

AOE must be distinguished from other painful ear conditions, such as acute otitis media, because treatment and prevention are different. Although both commonly are caused by bacteria (particularly *Pseudomonas aeruginosa* or *Staphylococcus*

species in the case of AOE), uncomplicated cases of AOE usually respond favorably to topical antimicrobials (with or without a topical corticosteroid) (3,8). Systemic antimicrobials usually are not indicated unless the AOE infection is complicated by an associated cellulitis of the surrounding skin, or other conditions (e.g., diabetes or immunosuppression) (3,4). Although AOE generally is a mild illness, it is a frequently diagnosed condition responsible for a substantial health-care burden, with estimated costs of \$0.5 billion and nearly 600,000 hours of clinicians' time annually. Development and dissemination of prevention messages potentially could lower the incidence of AOE and reduce the health-care burden.

The findings in this report are subject to at least two limitations. First, return visits for the same illness episode could not be excluded, and 3.6% of ambulatory-care visits for AOE resulted in referral, leading to a potential overestimate of AOE incidence; however, because AOE generally responds quickly to appropriate treatment, the proportion of return visits likely was minimal.^{§§} Regardless, each visit (whether initial or return) places a burden on the health-care system in health-care costs and clinicians' time. Finally, this analysis used a commercial insurance database to determine average costs. Visit costs might differ for persons with a different insurance provider (i.e., Medicaid or Medicare) or persons without insurance. Overall AOE costs likely are higher than estimated because visits to federal facilities and inpatient visits were not included in the analysis, nor were additional costs such as lost wages, school absence, or caretakers' time.

With the substantial costs imposed by AOE in health-care expenditures and clinicians' time, prevention of AOE could yield considerable savings. Few studies exist on AOE prevention, and controlled trials of potential prevention measures are needed. Current clinical recommendations are intended to reduce factors known to increase risk for AOE, such as prolonged water exposure and trauma to the skin of the ear canal (1,2,4,5,9). Prevention messages emphasize exclusion of water from the ear canal, drying ears thoroughly after water exposure, and avoiding insertion of solid objects into the ear canal (Box). Clinicians also might consider recommending the use of alcohol-based ear solutions after water exposure for persons with recurring episodes of AOE. Given that AOE's seasonality coincides with the traditional summer swim season (Memorial Day through Labor Day), prevention messages should be directed at swimmers. To optimize their effectiveness, these messages should be stressed before and during the summer swim season and target swimmers in the South,

^{§§} In the MarketScan database used for average cost estimation, approximately 1.5% of patients had both an ED and ambulatory-care visit for AOE, and some repeat visits by the same person might have been accounted for by a new infection episode rather than a return visit for the same infection.

BOX. Preventing acute otitis externa (AOE) (swimmer's ear)*

Keep your ears as dry as possible.

- Use a bathing cap, ear plugs, or custom-fitted swim molds when swimming to keep water out of your ears.

Dry your ears thoroughly after swimming or showering.

- Use a towel to dry your ears well.
- Tilt your head to hold each ear facing down to allow water to escape the ear canal.
- Pull your earlobe in different directions while your ear is faced down to help water drain out.
- If you still have water in your ears, consider using a hair dryer to move air within the ear canal.
 - Be sure the hair dryer is on the **lowest** heat and speed/fan setting.
 - Hold the hair dryer several inches from your ear.

Do not put objects in your ear canal (including cotton-tip swabs, pencils, paperclips, or fingers).

Do not try to remove ear wax. Ear wax helps protect your ear canal from infection.

- If you think your ear canal is blocked by ear wax, consult your health-care provider rather than trying to remove it yourself.

Consult your health-care provider about using commercial, alcohol-based ear drops or a 1:1 mixture of rubbing alcohol and white vinegar after swimming.

- Persons with ear tubes, damaged ear drums, outer ear infection, or ear drainage (pus or liquid coming from the ear) should not use drops.

Consult your health-care provider if your ears are itchy, flaky, swollen, or painful, or if you have drainage from your ears.

Ask your pool or hot tub operator if disinfectant and pH levels are checked at least twice per day.

- Hot tubs and pools with proper disinfectant and pH levels are less likely to spread germs.
- Use pool test strips to check the pool or hot tub yourself for adequate disinfectant and pH levels.

* Conclusive published evidence of the effectiveness of any intervention for the prevention of AOE is lacking. The prevention recommendations in this box are the consensus of three experts consulted by CDC staff: Michael T. Brady, MD, representing the American Academy of Pediatrics and Evelyn A. Kluka, MD, and Ken Kazahaya, MD, both representing the American Academy of Otolaryngology – Head and Neck Surgery. Additional information is available at <http://www.cdc.gov/healthywater/swimming/rwi/illnesses/swimmers-ear.html>.

Northeast, and Midwest, particularly those aged 5–14 years, and their caregivers. Additionally, pool operators can help prevent transmission of *Pseudomonas* and other common causes of infectious AOE in treated recreational water venues (e.g., pools, interactive fountains, and water parks) by maintaining proper chlorine and pH levels (10).

Acknowledgments

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References

1. Agius AM, Pickles JM, Burch KL. A prospective study of otitis externa. *Clin Otolaryngol* 1992;17:150–4.
2. Calderon R, Mood EW. An epidemiological assessment of water quality and "swimmer's ear." *Arch Environ Health* 1982;37:300–5.
3. Kaushik V, Malik T, Saeed SR. Interventions for acute otitis externa. *Cochrane Database of Systemic Reviews* 2010;1. Available at <http://onlinelibrary.wiley.com/doi/10.1002/14651858.cd004740>. Accessed May 12, 2011.
4. Rosenfeld RM, Brown L, Cannon CR, et al. Clinical practice guideline: acute otitis externa. *Otolaryngol Head Neck Surg* 2006;134:S4–23.
5. Springer GL. Fresh water swimming as a risk factor for otitis externa: a case-control study. *Arch Environ Health* 1985;40:202–6.
6. McCoy SI, Zell ER, Besser RE. Antimicrobial prescribing for otitis externa in children. *Pediatr Infect Dis J* 2004;23:181–3.
7. Halpern MT, Palmer CS, Seidlin M. Treatment patterns for otitis externa. *J Am Board Fam Pract* 1999;12:1–7.
8. Rosenfeld RM, Singer M, Wasserman JM, Stinnett. Systematic review of topical antimicrobial therapy for acute otitis externa. *Otolaryngol Head Neck Surg* 2006;134:S24–48.
9. Nussinovitch M, Rimon A, Volovitz B, Raveh E, Prais D, Amir J. Cotton-tip applicators as a leading cause of otitis externa. *Int J Pediatr Otorhinolaryngol* 2004;68:433–5.
10. CDC. Surveillance for waterborne disease and outbreaks associated with recreational water use and other aquatic facility-associated health events—United States, 2005–2006. *MMWR* 2008;57(No. SS-9).

Reasons for Not Seeking Eye Care Among Adults Aged ≥ 40 Years with Moderate-to-Severe Visual Impairment — 21 States, 2006–2009

In 2000, an estimated 3.4 million U.S. residents aged ≥ 40 years were blind or visually impaired (1). Vision problems place a substantial burden on individuals, caregivers, health-care payers, and the U.S. economy, with the total cost estimated at \$51.4 billion annually (2). Although regular comprehensive eye examinations are essential for timely treatment of eye disease to maintain vision health, a previous study has shown that substantial percentages of persons do not seek eye care, despite having visual impairment (3). To ascertain why adults aged ≥ 40 years with moderate-to-severe visual impairment did not seek eye care in the preceding year, CDC analyzed data for 21 states from 2006–2009 Behavioral Risk Factor Surveillance System (BRFSS) surveys. This report summarizes the results of that analysis, which found that eye-care cost or lack of insurance (39.8%) and perception of no need (34.6%) were the most common reasons given for not seeking eye care. Among those aged 40–64 years, cost or lack of health insurance was the most common reason (42.8%); among those aged ≥ 65 years, the most common reason was no need (43.8%). Identifying the reasons for unmet eye-care needs might enable development of targeted interventions to improve vision health among those with moderate-to-severe visual impairment.

BRFSS is an annual, state-based, random-digit-dialed telephone survey of the noninstitutionalized U.S. civilian population aged ≥ 18 years that provides sociodemographic and other information on health behaviors, chronic illness, and access to health care. For this report, CDC analyzed data from the BRFSS Vision Impairment and Access to Eye Care Module, which was implemented for at least 1 year during 2006–2009 by 21 states.* Median response rates among states for BRFSS during that period ranged from 48.2% to 52.5%; median cooperation rates ranged from 73.3% to 75.0%.†

The study sample consisted of 11,503 adults aged ≥ 40 years with self-reported moderate-to-severe visual impairment who had not visited an eye-care professional in the previous year; the sample constituted 6.96% of those interviewed (6.93% weighted). Prevalences for the 21 states overall and for each individual state were calculated from aggregate data collected during the 4-year study period, regardless of whether a state

had 1, 2, 3, or 4 years of data. Data were analyzed using statistical software to account for the complex sampling design. Estimates were weighted to account for individual selection probabilities, nonresponse, and poststratification. Chi-square testing was used to determine statistically significant differences ($p < 0.05$).

Self-reported visual impairment was defined using two questions: “How much difficulty, if any, do you have in recognizing a friend across the street?” and “How much difficulty, if any, do you have reading print in a newspaper, magazine, recipe, menu, or numbers on the telephone?” Those who answered “moderate difficulty,” “extreme difficulty,” or “unable to do because of eyesight” to either of these questions were classified as having moderate-to-severe visual impairment. Respondents also were asked if they had been told by an eye doctor or other health-care professional that they had cataract, glaucoma, age-related macular degeneration, or diabetic retinopathy. Those responding affirmatively were classified as having “any age-related eye disease.”

Respondents were asked when was the last time they had their eyes examined by any doctor or eye-care provider. Those reporting > 1 year also were asked the main reason for not visiting an eye-care professional in the past 12 months. The seven possible responses were classified into the following four categories: 1) “cost or lack of insurance”; 2) “have not thought of it” or “no reason to go (no problem)”; 3) “do not have/know an eye doctor,” “too far/no transportation,” or “could not get an appointment”; and 4) “other.”

Overall, the most common reason given for not seeking eye care among those with moderate-to-severe visual impairment was cost or lack of insurance (39.8%), followed by no need (34.6%), other (21.1%), and no eye doctor, no transportation, or could not get an appointment (4.5%) (Table 1). The percentage of those reporting cost or lack of insurance as the main reason was greater among adults aged 40–64 years than adults aged ≥ 65 years (42.8% versus 23.3%, $p < 0.001$). However, the percentage of those reporting no need to go as the main reason was greater among adults aged ≥ 65 years than those aged 40–64 years (43.8% versus 32.9%, $p < 0.001$). A greater percentage of men than women reported no need to go (41.7% versus 28.7%, $p = 0.005$), and a greater percentage of those with no age-related eye disease reported no need to go than those with any age-related eye disease (36.9% versus 28.2%, $p = 0.001$) (Table 1).

* Alabama, Arizona, Colorado, Connecticut, Florida, Georgia, Indiana, Iowa, Kansas, Maryland, Massachusetts, Missouri, Nebraska, New Mexico, New York, North Carolina, Ohio, Tennessee, Texas, West Virginia, and Wyoming.

† The response rate is the percentage of persons who completed interviews among all eligible persons, including those who were not successfully contacted. The cooperation rate is the percentage of persons who completed interviews among all eligible persons who were contacted.

Morbidity and Mortality Weekly Report

TABLE 1. Prevalence of reasons for not seeking eye care among adults aged ≥40 years with moderate-to-severe visual impairment,* by selected characteristics — Behavioral Risk Factor Surveillance System, 21 states, 2006–2009

Characteristic	Cost/Insurance		No need [†]		No eye doctor/travel/appointment [‡]		Other	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Overall	39.8	(38.0–41.5)	34.6	(32.9–36.3)	4.5	(3.9–5.2)	21.1	(19.8–22.5)
Age group (yrs)								
40–64	42.8	(40.8–44.8)	32.9	(31.1–34.8)	4.0	(3.4–4.8)	20.3	(18.8–21.8)
≥65	23.3	(20.2–26.7)	43.8	(40.2–47.5)	7.3	(5.8–9.2)	25.6	(22.3–29.3)
Sex								
Men	33.4	(30.6–36.3)	41.7	(38.9–44.6)	3.5	(2.8–4.5)	21.4	(19.2–23.7)
Women	45.1	(43.0–47.2)	28.7	(26.9–30.5)	5.3	(4.5–6.3)	20.9	(19.2–22.7)
Race/Ethnicity								
White, non-Hispanic	37.7	(35.7–39.8)	36.8	(34.8–38.8)	3.9	(3.4–4.6)	21.6	(20.0–23.3)
Black, non-Hispanic	41.0	(36.7–45.5)	32.4	(28.2–37.0)	6.2	(4.5–8.4)	20.4	(17.1–24.2)
Hispanic	51.1	(45.3–56.8)	23.6	(19.3–28.6)	7.2	(4.6–1.9)	18.1	(14.2–22.9)
Other	41.0	(32.0–50.6)	32.3	(22.9–43.3)	3.5	(2.0–6.0)	23.3	(16.6–31.5)
Education								
Less than high school diploma	54.1	(49.8–58.4)	24.3	(20.5–28.4)	5.7	(4.1–7.7)	15.9	(13.2–19.1)
High school diploma	41.5	(38.5–44.5)	35.0	(32.3–37.7)	3.8	(3.0–4.7)	19.7	(17.7–21.9)
More than high school diploma	32.7	(30.3–35.2)	38.4	(35.9–41.0)	4.6	(3.7–5.7)	24.2	(22.1–26.6)
Income								
<\$35,000	55.9	(53.4–58.4)	24.1	(22.2–26.2)	4.3	(3.5–5.2)	15.7	(14.1–17.5)
≥\$35,000	22.3	(20.3–24.4)	45.8	(43.2–48.5)	4.6	(3.7–5.7)	27.3	(25.0–29.8)
Health insurance coverage								
Yes	30.2	(28.4–32.0)	39.9	(38.1–41.8)	5.1	(4.4–5.9)	24.7	(23.1–26.4)
No	70.9	(67.0–74.5)	17.3	(14.2–20.8)	2.6	(1.6–4.3)	9.2	(7.3–11.6)
Eye-care insurance coverage								
Yes	19.6	(17.7–21.7)	44.8	(42.2–47.4)	6.2	(5.2–7.4)	29.4	(27.1–31.7)
No	55.2	(52.8–57.6)	26.9	(24.9–29.1)	3.2	(2.5–4.1)	14.7	(13.1–16.3)
Any age-related eye disease[§]								
Yes	39.8	(36.2–43.5)	28.2	(25.2–31.3)	6.7	(5.2–8.5)	25.4	(22.1–29.0)
No	39.4	(37.4–41.5)	36.9	(34.9–38.8)	4.0	(3.4–4.7)	19.7	(18.3–21.2)

Abbreviation: CI = confidence interval.

* Based on responses to the following two questions: “How much difficulty, if any, do you have in recognizing a friend across the street?” and “How much difficulty, if any, do you have reading print in newspapers, magazines, recipes, menus, or numbers on the telephone?” Those who answered “moderate difficulty,” “extreme difficulty,” or “unable to do because of eyesight” to either of the questions were classified as having moderate-to-severe visual impairment.

[†] Includes the following responses: “no reason to go (no problem)” or “have not thought of it.”

[‡] Includes the following responses: “do not have/know an eye doctor,” “too far, no transportation,” or “could not get appointments.”

[§] Respondents were asked whether they “had been told by an eye doctor or other health-care professional” that they had cataract, glaucoma, age-related macular degeneration, or diabetic retinopathy.

Among states, the percentage giving cost or lack of insurance as the main reason for not seeking eye care ranged from 21.6% (Massachusetts) to 60.4% (Tennessee) among those aged 40–64 years and from 8.9% (Massachusetts) to 48.0% (Tennessee) among those aged ≥65 years. The percentage reporting no need ranged from 25.4% (Florida) to 41.9% (Arizona) among those aged 40–64 years and from 29.7% (West Virginia) to 61.0% (Massachusetts) among those aged ≥65 years (Table 2).

Reported by

Chiu-Fang Chou, DrPH, Cheryl E. Sherrod, Xinzhi Zhang, MD, PhD, Kai McKeever Bullard, PhD, John E. Crews, DPA, Lawrence Barker, PhD, Jinan B. Saaddine, MD, Div of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, CDC. **Corresponding contributor:** Chiu-Fang Chou, CDC, cchou@cdc.gov, 770-488-1267.

Editorial Note

The data in this report support previous findings suggesting that lack of health insurance coverage is a major reason why persons with at least some self-reported visual impairment do not seek eye care (4). The data further indicate that the main reasons for not seeking eye care differ by age, sex, the presence of eye disease, and state of residence among persons with moderate-to-severe visual impairment. The large proportion of persons aged ≥65 years reporting no need as their main reason for not seeking care is of concern because this population has the highest prevalence of visual impairment (4). A possible reason for this is that older adults might regard impairment as a normal part of aging (5).

A previous study also has shown that persons often are not aware of eye health and the need for routine eye examinations because of lack of attention to eye care from primary-care

Morbidity and Mortality Weekly Report

TABLE 2. Prevalence of reasons for not seeking eye care among adults aged ≥40 years with moderate-to-severe visual impairment,* by state and age group — Behavioral Risk Factor Surveillance System, 21 states, 2006–2009

State	40–64 yrs								≥65 yrs							
	Cost/Insurance		No need†		No eye doctor/travel/appointment‡		Other		Cost/Insurance		No need		No eye doctor/travel/appointment		Other	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Alabama	47.1	(42.4–51.9)	31.9	(27.7–36.5)	4.4	(3.1–6.3)	16.5	(13.4–20.2)	20.4	(14.7–27.6)	44.6	(35.7–53.9)	10.1	(5.8–17.1)	24.9	(18.7–32.4)
Arizona	34.0	(23.4–46.4)	41.9	(30.2–54.7)	3.0	(1.2–7.6)	21.0	(12.8–32.5)	10.0	(4.0–23.2)	49.5	(30.7–68.5)	13.3	(5.9–27.0)	27.2	(11.8–50.9)
Colorado	40.0	(34.0–46.3)	38.2	(32.4–44.4)	2.4	(1.2–4.8)	19.4	(15.1–24.6)	16.6	(9.5–27.4)	42.4	(29.9–55.9)	4.5	(1.4–13.9)	36.5	(25.0–49.7)
Connecticut	27.7	(22.4–33.7)	33.3	(27.3–39.9)	4.9	(2.9–8.2)	34.1	(27.9–40.8)	13.5	(7.6–22.9)	49.1	(37.9–60.3)	10.2	(5.6–18.0)	27.2	(18.1–38.7)
Florida	49.8	(42.4–57.3)	25.4	(19.5–32.5)	4.3	(2.1–8.5)	20.5	(15.4–26.7)	25.4	(11.9–46.4)	34.1	(21.0–50.1)	10.2	(3.6–25.6)	30.3	(17.5–47.1)
Georgia	43.9	(39.4–48.5)	31.1	(27.1–35.3)	3.2	(2.0–5.1)	21.9	(18.2–26.0)	25.8	(18.5–34.7)	44.7	(35.8–53.8)	8.2	(4.3–15.2)	21.3	(15.1–29.2)
Indiana	51.0	(45.9–56.1)	30.5	(25.9–35.4)	2.9	(1.6–5.2)	15.6	(12.3–19.7)	32.4	(24.7–41.3)	46.6	(37.5–56.0)	3.7	(1.5–8.9)	17.2	(11.1–25.7)
Iowa	39.1	(33.2–45.3)	38.3	(32.3–44.6)	2.7	(1.3–5.4)	19.9	(15.2–25.6)	22.8	(15.2–32.8)	52.9	(42.1–63.4)	7.4	(3.3–15.7)	16.9	(10.6–26.0)
Kansas	42.0	(36.4–47.8)	39.2	(33.5–45.1)	3.8	(2.2–6.5)	15.1	(11.2–20.0)	20.6	(13.7–29.8)	43.8	(33.5–54.6)	11.6	(6.6–19.5)	24.1	(15.3–35.8)
Maryland	28.6	(20.6–38.3)	36.6	(27.3–47.1)	5.5	(2.2–13.3)	29.2	(21.3–38.6)	13.8	(5.3–31.5)	51.9	(30.7–72.4)	9.4	(2.8–27.3)	25.0	(9.7–50.9)
Massachusetts	21.6	(13.8–32.1)	40.2	(29.8–51.6)	9.3	(4.8–17.2)	28.9	(19.9–40.1)	8.9	(3.1–22.9)	61.0	(41.6–77.4)	4.9	(0.8–24.3)	25.2	(12.0–45.4)
Missouri	40.0	(33.2–47.3)	40.0	(32.9–47.6)	2.1	(1.0–4.4)	17.8	(13.0–24.0)	19.3	(10.5–32.7)	53.2	(40.3–65.8)	7.7	(3.2–17.7)	19.8	(11.3–32.2)
Nebraska	41.7	(33.7–50.3)	38.9	(31.1–47.4)	2.4	(1.1–5.0)	17.0	(12.3–23.0)	17.8	(10.6–28.4)	40.5	(30.6–51.2)	4.3	(1.6–11.0)	37.4	(27.2–48.8)
New Mexico	50.6	(44.1–57.0)	38.7	(32.7–45.1)	7.0	(4.5–10.7)	3.7	(2.0–6.8)	26.2	(17.0–38.0)	57.9	(46.1–68.8)	11.2	(6.0–19.9)	4.8	(1.6–13.2)
New York	31.5	(27.2–36.3)	36.4	(31.8–41.3)	5.0	(3.3–7.5)	27.0	(22.9–31.5)	20.8	(14.0–29.8)	42.3	(33.6–51.6)	8.2	(4.1–15.7)	28.7	(21.2–37.5)
North Carolina	48.4	(43.2–53.6)	28.8	(24.6–33.4)	3.4	(1.9–5.9)	19.5	(15.6–24.1)	28.8	(21.5–37.5)	46.0	(37.3–55.0)	5.7	(2.5–12.5)	19.4	(13.4–27.3)
Ohio	42.6	(38.2–47.1)	28.5	(24.7–32.7)	3.2	(2.1–5.1)	25.6	(21.7–30.0)	26.5	(18.2–36.8)	46.2	(37.3–55.4)	6.4	(3.5–11.3)	20.9	(15.4–27.7)
Tennessee	60.4	(51.7–68.5)	27.7	(20.7–35.9)	2.8	(1.1–6.6)	9.2	(5.2–15.9)	35.9	(21.4–53.6)	33.9	(19.4–52.1)	6.0	(1.5–21.2)	24.2	(12.4–42.1)
Texas	51.1	(42.4–59.7)	30.9	(23.4–39.5)	4.3	(2.3–7.7)	13.8	(8.9–20.7)	25.4	(13.9–41.8)	34.1	(20.0–51.6)	5.6	(2.4–12.2)	34.9	(20.2–53.3)
West Virginia	59.0	(50.2–67.2)	27.5	(20.2–36.1)	4.8	(2.1–10.4)	8.8	(5.3–14.3)	48.0	(31.5–65.0)	29.7	(17.3–46.0)	1.0	(0.1–6.8)	21.3	(10.9–37.5)
Wyoming	34.2	(28.6–40.4)	41.1	(35.2–47.3)	3.0	(1.7–5.5)	21.6	(17.1–27.0)	23.1	(15.3–33.2)	52.4	(41.7–62.9)	2.2	(0.7–6.9)	22.4	(14.5–32.9)
Total	42.8	(40.8–44.8)	32.9	(31.1–34.8)	4	(3.4–4.8)	20.3	(18.8–21.8)	23.3	(20.2–26.7)	43.8	(40.2–47.5)	7.3	(5.8–9.2)	25.6	(22.3–29.3)

Abbreviation: CI = confidence interval.

* Based on responses to the following two questions: "How much difficulty, if any, do you have in recognizing a friend across the street?" and "How much difficulty, if any, do you have reading print in newspapers, magazines, recipes, menus, or numbers on the telephone?" Those who answered "moderate difficulty," "extreme difficulty," or "unable to do because of eyesight" to either of the questions were classified as having moderate-to-severe visual impairment.

† Includes the following responses: "no reason to go (no problem)" or "have not thought of it."

‡ Includes the following responses: "do not have/know an eye doctor," "too far, no transportation," or "could not get appointments."

providers (6). Recommendations from primary-care providers can influence patients to receive eye-care services; persons who had visual screening during routine physical examinations had better eye health because of reminders to visit eye specialists (6,7). Public health interventions aimed at heightening awareness among both adults aged ≥65 years and health-care providers might increase utilization rates among persons with age-related eye diseases or chronic diseases that affect vision such as diabetes.

In this study, men and women reported different main reasons for not seeking care. Men were more likely than women to report no need to seek eye care, and women were more likely than men to report cost or lack of insurance as their main reason. This finding corresponds with results from a previous study showing that women had less financial access to care than men (8). Reasons for not seeking eye care also differed by eye disease status. Not surprisingly, persons with eye disease were less likely to report no need as the main reason for not seeking care. Instead, cost or lack of insurance was the most common reason for those with eye diseases. Previous research has found that populations without insurance that are at high risk for eye diseases are least likely to seek preventive eye care at the recommended frequency (9).

Differences also were observed among states. Among the 21 states, the percentage of respondents reporting cost or lack of insurance as the main reason for not seeking eye care was lowest for both adults aged 40–64 years and ≥65 years in Massachusetts, the state with the smallest proportion of residents with no health insurance (10). Surveys such as BRFSS that provide state-level data can help policy makers identify potential areas of unmet health-care needs.

The findings in this report are subject to at least three limitations. First, BRFSS data are self-reported, and their accuracy might have been affected by recall, social desirability, and other biases. Second, perceived visual impairment might not be highly correlated with clinically diagnosed impairment using visual acuity measurements. Finally, only 21 states administered the vision module during the study period, so the results might not be representative of the entire U.S. population.

Reducing visual impairment and improving quality of life among persons with impairment should be public health priorities. By determining reasons why persons with moderate-to-severe visual impairment do not seek eye care, this report can help shape policy, develop targeted interventions, and disseminate effective public health messages.

Morbidity and Mortality Weekly Report

What is already known on this topic?

Studies have shown that substantial percentages of persons do not seek eye care, despite having visual impairment.

What is added by this report?

The main reasons for not seeking eye care were found to be cost/lack of insurance or a perception of no need. The prevalence of these reasons differed by age, sex, the presence of eye disease, and state of residence; among those aged 40–64 years, cost or lack of health insurance was the most common reason, whereas persons aged ≥65 years reported no need to seek eye care, and women were more likely than men to report cost or lack of insurance as their main reason for not seeking care.

What are the implications for public health practice?

Understanding why eye-care needs go unmet might provide policy makers with information that will enable them to target those populations at greatest risk and help reduce visual impairment. Surveys that provide state-level data can help policy makers identify potential areas of unmet health-care needs.

References

1. The Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;122:477–85.
2. Prevent Blindness America. The economic impact of vision problems. Available at http://www.preventblindness.org/research/impact_of_Vision_Problems.pdf. Accessed May 16, 2011.
3. Lee DJ, Lam BL, Arora S, et al. Reported eye care utilization and health insurance status among US adults. *Arch Ophthalmol* 2009;127:303–10.
4. Buch H, Vinding T, la Cour M, Appleyard M, Jensen GB, Nielsen NV. Prevalence and causes of visual impairment and blindness among 9980 Scandinavian adults: the Copenhagen City Eye Study. *Ophthalmology* 2004;111:53–61.
5. US Preventive Services Task Force. Screening for impaired visual acuity in older adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;151:37–43.
6. Alexander RL Jr., Miller NA, Cotch MF, Janiszewski R. Factors that influence the receipt of eye care. *Am J Health Behav* 2008;32:547–56.
7. Strahlman E, Ford D, Whelton P, Sommer A. Vision screening in a primary care setting. A missed opportunity? *Arch Intern Med* 1990; 150:2159–64.
8. Nelson DE, Thompson BL, Bland SD, Rubinson R. Trends in perceived cost as a barrier to medical care, 1991–1996. *Am J Public Health* 1999; 89:1410–3.
9. Zhang X, Saaddine JB, Lee PP, et al. Eye care in the United States: do we deliver to high-risk people who can benefit the most from it? *Arch Ophthalmol* 2007;125:411–8.
10. Long SK, Masi PB. Access and affordability: an update on health reform in Massachusetts, fall 2008. *Health Aff (Millwood)* 2009;28w578–87.

Arthritis as a Potential Barrier to Physical Activity Among Adults with Obesity — United States, 2007 and 2009

Adults with obesity are less likely than adults without obesity to follow physical activity recommendations, despite the known benefits of physical activity for weight loss and weight maintenance (1,2). Arthritis is a common comorbidity of adults with obesity (3), and arthritis-related joint pain and functional limitation might contribute substantially to low rates of physical activity among adults with obesity. CDC analyzed combined 2007 and 2009 Behavioral Risk Factor Surveillance System (BRFSS) data for adults aged ≥ 18 years to estimate overall and state-specific prevalence of 1) self-reported doctor-diagnosed arthritis among adults with self-reported obesity, and 2) prevalence of self-reported physical inactivity among adults with obesity by arthritis status. This report describes the results of that analysis, which indicated that, overall, arthritis affected 35.6% of adults with obesity. After adjusting for age, sex, race/ethnicity, and education level, adults with obesity and arthritis were 44% more likely to be physically inactive compared with persons with obesity but without arthritis. Among states, the median prevalence of arthritis among adults with obesity was 35.6%. In every state/area except Guam, the prevalence of physical inactivity among adults with obesity was at least 5 percentage points higher (range: 5.4–15.9 percentage points) among persons with arthritis than those without arthritis. Arthritis might be a special barrier to increasing physical activity among many adults with obesity. Safe and effective self-management education and physical activity programs for adults with arthritis exist to address this barrier, are offered in many communities, and can help adults with obesity and arthritis become more physically active.

BRFSS is a state-based, random-digit-dialed telephone survey of the noninstitutionalized U.S. civilian population aged ≥ 18 years. Data were collected from the 50 states, the District of Columbia (DC), Puerto Rico, Guam, and the U.S. Virgin Islands.* Response rates were calculated using Council of American Survey and Research Organizations (CASRO) guidelines; for 2007 and 2009, respectively, the numbers of respondents were 430,912 and 432,607, median response rates were 50.6% and 52.5%, and median cooperation rates were 72.1% and 75.0%.† Body mass index (BMI) was calculated from self-reported height and weight; obesity was defined as

a BMI ≥ 30 kg/m². For consistency with previous analyses (4), participants reporting weight ≥ 500 pounds or height ≥ 7 feet or < 3 feet were excluded. Doctor-diagnosed arthritis was defined based on a “yes” response to the question “Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?” Physical activity level was determined from six questions on the frequency and duration of participation in nonoccupational activities of moderate and vigorous intensity. Persons reporting no participation in these activities were classified as physically inactive.

Yearly sampling weights divided by 2 were applied to generate average annual point estimates representative of each state/area. Taylor series linearization method was used to account for the complex sample design and generate 95% confidence intervals (CIs). Chi-square tests were used to determine statistically significant differences ($p < 0.05$) in characteristics by disease status. Logistic regression was used to assess the association between self-reported doctor-diagnosed arthritis and physical inactivity among persons with obesity. Unadjusted state-level prevalence estimates are reported to provide state and local health departments and other partners with data that can be used to help guide future state-level planning, partnership building, and advocacy efforts.

Analysis of the combined 2007 and 2009 data indicated that overall, 9.3% of respondents had both obesity and arthritis, 16.9% had obesity only, and 17.3% had arthritis only (Table 1); arthritis prevalence among adults with obesity was 35.6%. Women were significantly more likely to have both arthritis and obesity or arthritis only. Older age was associated with a significantly higher prevalence of both arthritis and obesity. Compared with other racial/ethnic groups, non-Hispanic blacks had a significantly higher prevalence of both arthritis and obesity, non-Hispanic blacks and Hispanics had a significantly higher prevalence of obesity only, and non-Hispanic whites had a significantly higher prevalence of arthritis only. Higher education level was associated with a lower prevalence of both obesity and arthritis, obesity only, and arthritis only.

Prevalence of physical inactivity was highest among those with both arthritis and obesity (22.7%) compared with arthritis only (16.1%), obesity only (13.5%), and neither condition (9.4%) (Figure). In logistic regression models adjusting for age, sex, race/ethnicity, and education level, adults with both obesity and arthritis were 44% more likely to be physically inactive than adults without arthritis (odds ratio = 1.44; CI = 1.37–1.52).

* BRFSS survey data are available at http://www.cdc.gov/brfss/technical_infodata/surveydata.htm.

† The response rate is the percentage of persons who completed interviews among all eligible persons, including those who were not successfully contacted. The cooperation rate is the percentage of persons who completed interviews among all eligible persons who were contacted.

Morbidity and Mortality Weekly Report

TABLE 1. Weighted percentage of adults aged ≥18 years who reported both obesity* and arthritis,† obesity only, arthritis only, or neither condition, by selected characteristics — Behavioral Risk Factor Surveillance System, combined 50 States and District of Columbia, 2007 and 2009

Characteristic	Unweighted no.	Both obesity and arthritis		Obesity only		Arthritis only		Neither condition	
		%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Total	789,460[§]	9.3	(9.2–9.4)	16.9	(16.7–17.1)	17.3	(17.1–17.4)	56.5	(56.2–56.7)
Sex									
Men	305,395	8.1	(7.9–8.2)	18.9	(18.6–19.2)	14.5	(14.3–14.7)	58.6	(58.2–58.9)
Women	484,065	10.6	(10.4–10.7)	14.9	(14.7–15.2)	20.0	(19.8–20.2)	54.4	(54.2–54.7)
Age group (yrs)									
18–44	221,360	4.0	(3.8–4.1)	20.5	(20.2–20.9)	6.7	(6.5–6.9)	68.8	(68.4–69.2)
45–64	329,296	14.3	(14.1–14.5)	16.4	(16.1–16.6)	21.3	(21.0–21.6)	48.1	(47.7–48.4)
≥65	238,804	15.2	(14.9–15.5)	7.4	(7.2–7.7)	40.2	(39.8–40.5)	37.2	(36.8–37.6)
Race/Ethnicity									
White, non-Hispanic	635,049	9.7	(9.6–9.8)	15.2	(15.0–15.4)	19.6	(19.4–19.8)	55.5	(55.3–55.7)
Black, non-Hispanic	59,045	12.5	(12.0–12.9)	24.0	(23.3–24.8)	13.3	(12.8–13.8)	50.2	(49.3–51.0)
Hispanic	45,744	6.3	(5.9–6.8)	23.3	(22.4–24.1)	9.0	(8.5–9.5)	61.4	(60.4–62.3)
Other	42,606	6.4	(6.1–6.8)	12.4	(11.7–13.1)	14.2	(13.5–14.9)	67.0	(66.0–68.0)
Education level (yrs)									
≤11	73,746	11.9	(11.5–12.4)	19.2	(18.5–20.0)	18.1	(17.5–18.6)	50.8	(49.9–51.7)
12	237,667	11.1	(10.8–11.3)	18.2	(17.8–18.6)	18.8	(18.5–19.1)	51.9	(51.5–52.4)
≥13	478,046	8.1	(8.0–8.2)	15.9	(15.7–16.1)	16.4	(16.2–16.6)	59.6	(59.3–59.8)

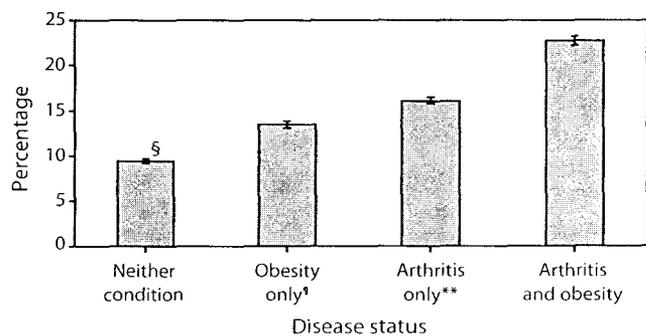
Abbreviation: CI = confidence interval.

* Obesity was calculated from self-reported height and weight and defined as a body mass index ≥30 kg/m².

† Doctor-diagnosed arthritis was defined based on a “yes” response to the question, “Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?”

§ Number of persons who provided a response for obesity and arthritis questions. Some categories might not add to total because of missing information on some demographic characteristics.

FIGURE. Weighted prevalence of physical inactivity among adults aged ≥18 years,* by disease status — Behavioral Risk Factor Surveillance System, United States,† 2007 and 2009



* Includes all respondents reporting no activity when asked six questions about frequency and duration of participation in nonoccupational activities of moderate and vigorous intensity (i.e., lifestyle activities). All other respondents were classified as active. Questions available at <http://www.cdc.gov/brfss/questionnaires/pdf-ques/2007brfss.pdf> and <http://www.cdc.gov/brfss/questionnaires/pdf-ques/2009brfss.pdf>.

† Includes all 50 states and District of Columbia.

§ 95% confidence interval.

§ Obesity was calculated from self-reported height and weight and defined as a body mass index ≥30 kg/m².

** Doctor-diagnosed arthritis was defined based on a “yes” response to the question, “Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?”

In state-specific analyses of adults with obesity, arthritis was common (median: 35.6%; range: 28.7% in California and Hawaii to 44.1% in West Virginia) (Table 2). Among adults with obesity, physical inactivity for those with arthritis in the 50 states and DC was higher (median: 21.2%; range: 14.3% in Wisconsin to 38.8% in Tennessee) than for those without arthritis (median: 12.4%; range: 7.5% in Utah to 29.9% in Tennessee); furthermore, prevalence of physical inactivity was at least 5 percentage points higher in every state.

Reported by

Jennifer M. Hootman, PhD, Louise B. Murphy, PhD, Charles G. Helmick, MD, Arthritis Program, Div of Adult and Community Health, National Center of Chronic Disease Prevention and Health Promotion; Kamil E. Barbour, PhD, EIS officer, CDC. **Corresponding contributor:** Kamil E. Barbour, CDC, 770-488-5145, kbarbour@cdc.gov.

Editorial Note

Arthritis and obesity are common chronic conditions affecting an estimated 50 million (3) and 72 million (4) U.S. adults, respectively. The findings in this report indicate that these conditions co-occur commonly (one in three adults with obesity also has arthritis) and might hinder the management of both conditions by limiting physical activity. Among adults with both obesity and arthritis, the adjusted likelihood of physical

Morbidity and Mortality Weekly Report

TABLE 2. Weighted prevalence of arthritis* and prevalence of physical inactivity† stratified by arthritis status among adults with obesity‡ aged ≥18 years, by state/area — Behavioral Risk Factor Surveillance System, United States,¶ 2007 and 2009 combined

State/Area	No. of respondents	Arthritis prevalence among adults with obesity			Physical inactivity prevalence among adults with obesity			
		Weighted no. (in 1,000s)**	%	(95% CI)	Without arthritis		With arthritis	
					%	(95% CI)	%	(95% CI)
Alabama	14,039	422	41.4	(39.2–43.6)	18.2	(15.6–21.1)	30.1	(27.3–33.1)
Alaska	4,984	44	35.6	(32.0–39.3)	10.0	(7.3–13.5)	19.0	(14.6–24.4)
Arizona	10,208	322	29.2	(26.1–32.6)	11.8	(9.0–15.2)	20.3	(16.5–24.7)
Arkansas	9,742	223	37.5	(35.0–40.0)	11.1	(9.0–13.6)	23.4	(20.6–26.4)
California	23,083	1,677	28.7	(26.9–30.6)	12.8	(11.0–14.9)	18.2	(15.5–21.3)
Colorado	23,864	208	33.3	(31.5–35.0)	8.6	(7.2–10.2)	17.4	(15.3–19.6)
Connecticut	14,019	187	35.5	(33.2–37.9)	11.8	(9.8–14.0)	18.9	(16.0–22.1)
Delaware	8,352	65	38.8	(36.1–41.7)	12.7	(10.3–15.6)	22.3	(18.8–26.3)
District of Columbia	7,861	31	35.0	(32.1–38.0)	12.4	(9.9–15.3)	26.0	(21.9–30.5)
Florida	51,604	1,063	32.7	(30.9–34.5)	14.9	(12.9–17.0)	27.5	(24.9–30.2)
Georgia	13,599	630	34.4	(32.2–36.6)	13.7	(11.3–16.5)	22.2	(19.5–25.1)
Hawaii	13,286	61	28.7	(26.5–31.1)	11.5	(9.6–13.7)	20.4	(17.1–24.2)
Idaho	10,705	86	33.7	(31.4–36.0)	8.6	(6.9–10.7)	18.4	(15.8–21.4)
Illinois	11,081	840	35.0	(32.9–37.2)	12.0	(10.0–14.3)	19.1	(16.5–21.9)
Indiana	15,279	501	39.8	(37.8–41.8)	14.0	(11.9–16.3)	22.9	(20.4–25.6)
Iowa	11,452	200	34.4	(32.4–36.4)	11.2	(9.5–13.2)	18.8	(16.5–21.3)
Kansas	27,407	186	33.9	(32.5–35.4)	12.4	(11.1–13.8)	22.7	(20.9–24.5)
Kentucky	16,560	381	43.1	(40.8–45.5)	19.4	(16.9–22.2)	32.0	(29.1–35.1)
Louisiana	15,566	334	34.5	(32.7–36.3)	19.5	(17.4–21.9)	33.9	(31.3–36.7)
Maine	14,912	98	38.7	(36.8–40.7)	9.8	(8.3–11.5)	20.0	(17.9–22.4)
Maryland	17,420	384	37.3	(35.3–39.2)	14.1	(12.0–16.5)	22.0	(19.6–24.5)
Massachusetts	38,238	353	36.1	(34.5–37.8)	13.3	(11.8–14.9)	22.1	(20.2–24.1)
Michigan	16,760	881	42.4	(40.6–44.2)	10.4	(8.8–12.1)	21.3	(19.4–23.4)
Minnesota	10,385	288	29.6	(27.5–31.8)	10.5	(8.8–12.4)	16.6	(14.3–19.3)
Mississippi	19,012	259	37.6	(36.0–39.3)	16.0	(14.3–17.8)	31.9	(29.7–34.2)
Missouri	10,320	489	40.1	(37.5–42.7)	11.5	(9.3–14.2)	21.2	(18.4–24.2)
Montana	13,613	59	37.5	(35.2–39.8)	9.4	(7.5–11.6)	15.9	(13.7–18.3)
Nebraska	26,932	124	36.6	(34.5–38.8)	12.2	(10.1–14.6)	20.5	(17.8–23.4)
Nevada	7,965	151	33.2	(29.8–36.7)	13.1	(10.3–16.7)	20.1	(15.7–25.3)
New Hampshire	11,979	86	35.1	(32.9–37.4)	9.2	(7.5–11.1)	20.7	(18.1–23.6)
New Jersey	19,626	499	35.4	(33.4–37.5)	15.8	(13.8–18.1)	27.8	(24.9–31.0)
New Mexico	15,443	116	33.7	(31.7–35.9)	11.9	(9.7–14.4)	18.4	(16.0–21.1)
New York	13,452	1,291	38.4	(36.3–40.6)	14.0	(11.7–16.7)	20.9	(18.5–23.5)
North Carolina	28,054	670	36.5	(34.8–38.3)	13.0	(11.4–14.8)	23.2	(21.2–25.4)
North Dakota	9,518	43	33.7	(31.4–36.0)	11.0	(9.1–13.3)	18.0	(15.1–21.2)
Ohio	21,003	965	41.3	(39.5–43.1)	11.8	(10.1–13.8)	23.1	(21.2–25.1)
Oklahoma	15,309	296	38.4	(36.6–40.2)	12.8	(11.2–14.6)	24.7	(22.5–27.0)
Oregon	9,248	235	35.5	(33.0–38.0)	10.9	(8.6–13.6)	17.8	(15.2–20.7)
Pennsylvania	22,409	1,088	43.3	(41.3–45.3)	13.3	(11.3–15.6)	19.7	(17.5–22.0)
Rhode Island	10,795	69	38.4	(35.9–40.9)	12.7	(10.6–15.2)	24.7	(21.8–27.8)
South Carolina	20,255	356	39.2	(37.1–41.2)	14.3	(12.4–16.3)	24.3	(21.8–26.9)
South Dakota	13,699	51	32.9	(30.8–35.0)	12.5	(10.5–14.8)	22.7	(20.1–25.6)
Tennessee	10,611	500	36.6	(34.0–39.2)	29.9	(26.5–33.7)	38.8	(34.8–42.9)
Texas	28,856	1,357	30.3	(28.7–31.9)	13.7	(12.1–15.6)	22.9	(20.8–25.2)
Utah	15,240	130	32.8	(30.8–34.8)	7.5	(6.0–9.3)	16.8	(14.3–19.6)
Vermont	13,600	39	37.8	(35.8–39.9)	9.4	(7.6–11.5)	18.9	(16.7–21.4)
Virginia	11,387	479	35.6	(33.0–38.3)	13.6	(10.0–18.4)	24.0	(20.8–27.5)
Washington	46,175	422	35.1	(33.9–36.3)	10.3	(9.3–11.4)	17.3	(16.0–18.7)
West Virginia	9,262	184	44.1	(42.0–46.3)	22.5	(20.0–25.3)	36.8	(33.8–39.8)
Wisconsin	11,988	390	36.2	(33.7–38.8)	7.9	(6.3–9.8)	14.3	(12.0–17.0)
Wyoming	12,218	32	35.2	(33.0–37.4)	10.8	(9.1–12.8)	17.2	(15.0–19.7)
Median††			35.6		12.4		21.2	
Puerto Rico	8,174	185	25.7	(23.6–27.8)	45.2	(41.8–48.6)	56.3	(52.0–60.5)
U.S. Virgin Islands	5,047	4	22.3	(19.8–25.1)	20.0	(17.0–23.4)	30.2	(24.3–36.9)
Guam	1,923	4	17.0	(13.3–21.5)	15.4	(11.4–20.6)	18.6	(11.0–29.7)

Abbreviation: CI = confidence interval.

* Obesity was calculated from self-reported height and weight and defined as a body mass index ≥30 kg/m².

† Physical activity level was determined from six questions that asked about frequency and duration of participation in nonoccupational activities of moderate and vigorous intensity; persons reporting no participation in such activities were classified as inactive (engaged in no nonoccupational physical activity); all others were classified as active.

‡ Doctor-diagnosed arthritis was defined based on a "yes" response to the question, "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?"

§ Includes all 50 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands.

** Weighted annual average number of adults with obesity who also have arthritis.

†† Does not include Puerto Rico, U.S. Virgin Islands, or Guam.

Morbidity and Mortality Weekly Report

What is already known on this topic?

Physical activity is a recommended intervention for adults with obesity, but arthritis might be a common comorbidity that limits physical activity.

What is added by this report?

Arthritis is common among U.S. adults with obesity (35.6%). Adults with obesity and arthritis were 44% more likely to be physically inactive compared with adults with obesity but without arthritis. In every state, physical inactivity prevalence was at least 5 percentage points higher (range: 5.4–15.9 percentage points) among adults with obesity and arthritis compared with adults with obesity only.

What are the implications for public health practice?

Addressing specific barriers to physical activity that arthritis presents for adults with obesity might help a substantial proportion of adults with both conditions to reduce activity limitations and improve health. Local, community-based, arthritis-appropriate interventions, including evidence-based physical activity and self-management education programs, can specifically address these barriers.

inactivity was 44% higher compared with that of adults with obesity but without arthritis; all state-specific estimates were consistent with these results. These findings suggest that among many persons with obesity, arthritis might be an additional barrier to physical activity.

In addition to obesity, arthritis also has been implicated as a potential barrier to physical activity among persons with heart disease (5) and diabetes (6), conditions often occurring in the same persons. Adults with obesity, and those with heart disease and diabetes, like those without these conditions, face the usual barriers to physical activity, such as lack of motivation and time, competing responsibilities, and difficulty finding an enjoyable activity (7). Persons with arthritis have special barriers to physical activity, including concerns about aggravating arthritis pain and causing further joint damage, and lack of knowledge about which types and amounts of physical activity will not exacerbate their arthritis (7). Health-care providers recommending physical activity for weight loss and weight maintenance should ask their patients about arthritis and related symptoms (e.g., pain and functional limitations) and consider appropriate exercise regimens for those with arthritis and obesity. Low-impact activities such as walking, swimming, and biking generally are safe and appropriate for adults with both obesity and arthritis and can have a role in weight loss and joint pain reduction. In a randomized trial of older adults with osteoarthritis, those with a combined diet and exercise intervention lost more weight than controls (an average of 5.7% of body mass compared with an average of 1.2% in controls) and had less pain and improved physical

function (8). Evidence-based physical activity programs, such as EnhanceFitness, the Arthritis Foundation Exercise Program, and the Arthritis Foundation Walk With Ease programs are offered in many communities.[§] These programs have proven to be safe and effective for persons with arthritis and specifically address arthritis-specific barriers to being physically active. In addition, self-management education programs such as The Arthritis Foundation Self-Help Program and the Chronic Disease Self-Management Program can help adults manage symptoms, communicate with their health-care provider, and safely increase physical activity. The CDC Arthritis Program funds 12 state programs to increase the availability of these evidence-based interventions.[¶] Wider implementation of these programs in service delivery systems in community and health-care settings would likely have a meaningful public health impact.

The findings in this report are subject to at least five limitations. First, arthritis, obesity, and physical activity level are self-reported in BRFSS and are not validated by direct measurement. Particularly, height and weight might be overreported or underreported (9); the exact magnitude of this bias is unknown. Second, occupational physical activity was not assessed. Therefore, some adults might have been classified as inactive, despite engaging in moderate-to-vigorous activity at work. Third, BRFSS excludes persons without landline telephones, persons in the military, and those residing in institutions. Estimates are weighted, which partially corrects for underrepresentation attributed to noncoverage of households without a landline telephone. These weights also correct for nonresponse. Fourth, these data are cross-sectional, so causality cannot be inferred directly. Finally, the unadjusted state-level prevalence estimates should not be used for state to state comparisons because they do not account for demographic characteristics (e.g., age) that might vary across states.

These are the first state-level estimates demonstrating the co-occurrence of arthritis and obesity and its association with physical inactivity. Reducing the impact of the obesity epidemic is a high priority for public health in general and for CDC, where addressing nutrition, physical activity, and obesity is one of six “winnable battles.”** Addressing the special barriers that arthritis presents to physical activity, a primary behavioral intervention for adults with obesity, might help a substantial proportion of adults with both conditions to reduce activity limitations and improve health.

[§] Additional information about CDC-recommended physical activity and self-management education programs is available at <http://www.cdc.gov/arthritis/interventions.htm>.

[¶] Additional information available at http://www.cdc.gov/arthritis/state_programs.htm.

** Additional information available at <http://www.cdc.gov/winnablebattles>.

Morbidity and Mortality Weekly Report

Health-care providers, by determining whether arthritis contributes to physical inactivity among their patients with obesity, can tailor their advice and recommendations, including referral to local arthritis-appropriate interventions that specifically address these barriers through proven physical activity and self-management education programs (10). In addition, greater integration of state and community environmental and policy efforts to address obesity and arthritis might reduce the burden of both conditions.

References

1. Cooper AR, Page A, Fox KR, Misson J. Physical activity patterns in normal, overweight and obese individuals using minute-by-minute accelerometry. *Eur J Clin Nutr* 2000;54:887-94.
2. Rippe JM, Hess S. The role of physical activity in the prevention and management of obesity. *J Am Diet Assoc* 1998;98(10 Suppl 2):S31-8.
3. CDC. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2007–2009. *MMWR* 2010;59:1261-5.
4. CDC. Vital signs: state-specific obesity prevalence among adults—United States, 2009. *MMWR* 2010;59:951-5.
5. CDC. Arthritis as a potential barrier to physical activity among adults with heart disease—United States, 2005 and 2007. *MMWR* 2009;58:165-9.
6. CDC. Arthritis as a potential barrier to physical activity among adults with diabetes—United States, 2005 and 2007. *MMWR* 2008;57:486-9.
7. Wilcox S, DerAnanian C, Abbott J, et al. Perceived exercise barriers, enablers, and benefits among exercising and nonexercising adults with arthritis: results from a qualitative study. *Arthritis Rheum* 2006;55:616-27.
8. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum* 2004;50:1501-10.
9. Merrill RM, Richardson JS. Validity of self-reported height, weight, and body mass index: findings from the National Health and Nutrition Examination Survey, 2001–2006. *Prev Chronic Dis* 2009;6:A121.
10. Brady TJ, Kruger J, Helmick CG, Callahan LF, Boutaugh ML. Intervention programs for arthritis and other rheumatic diseases. *Health Educ Behav* 2003;30:44-63.

Ten Great Public Health Achievements — United States, 2001–2010

During the 20th century, life expectancy at birth among U.S. residents increased by 62%, from 47.3 years in 1900 to 76.8 in 2000, and unprecedented improvements in population health status were observed at every stage of life (1). In 1999, *MMWR* published a series of reports highlighting 10 public health achievements that contributed to those improvements. This report assesses advances in public health during the first 10 years of the 21st century. Public health scientists at CDC were asked to nominate noteworthy public health achievements that occurred in the United States during 2001–2010. From those nominations, 10 achievements, not ranked in any order, have been summarized in this report.

Vaccine-Preventable Diseases

The past decade has seen substantial declines in cases, hospitalizations, deaths, and health-care costs associated with vaccine-preventable diseases. New vaccines (i.e., rotavirus, quadrivalent meningococcal conjugate, herpes zoster, pneumococcal conjugate, and human papillomavirus vaccines, as well as tetanus, diphtheria, and acellular pertussis vaccine for adults and adolescents) were introduced, bringing to 17 the number of diseases targeted by U.S. immunization policy. A recent economic analysis indicated that vaccination of each U.S. birth cohort with the current childhood immunization schedule prevents approximately 42,000 deaths and 20 million cases of disease, with net savings of nearly \$14 billion in direct costs and \$69 billion in total societal costs (2).

The impact of two vaccines has been particularly striking. Following the introduction of pneumococcal conjugate vaccine, an estimated 211,000 serious pneumococcal infections and 13,000 deaths were prevented during 2000–2008 (3). Routine rotavirus vaccination, implemented in 2006, now prevents an estimated 40,000–60,000 rotavirus hospitalizations each year (4). Advances also were made in the use of older vaccines, with reported cases of hepatitis A, hepatitis B, and varicella at record lows by the end of the decade. Age-specific mortality (i.e., deaths per million population) from varicella for persons age <20 years, declined by 97% from 0.65 in the prevaccine period (1990–1994) to 0.02 during 2005–2007 (5). Average age-adjusted mortality (deaths per million population) from hepatitis A also declined significantly, from 0.38 in the prevaccine period (1990–1995) to 0.26 during 2000–2004 (6).

Prevention and Control of Infectious Diseases

Improvements in state and local public health infrastructure along with innovative and targeted prevention efforts yielded significant progress in controlling infectious diseases. Examples

include a 30% reduction from 2001 to 2010 in reported U.S. tuberculosis cases and a 58% decline from 2001 to 2009 in central line-associated blood stream infections (7,8). Major advances in laboratory techniques and technology and investments in disease surveillance have improved the capacity to identify contaminated foods rapidly and accurately and prevent further spread (9–12). Multiple efforts to extend HIV testing, including recommendations for expanded screening of persons aged 13–64 years, increased the number of persons diagnosed with HIV/AIDS and reduced the proportion with late diagnoses, enabling earlier access to life-saving treatment and care and giving infectious persons the information necessary to protect their partners (13). In 2002, information from CDC predictive models and reports of suspected West Nile virus transmission through blood transfusion spurred a national investigation, leading to the rapid development and implementation of new blood donor screening (14). To date, such screening has interdicted 3,000 potentially infected U.S. donations, removing them from the blood supply. Finally, in 2004, after more than 60 years of effort, canine rabies was eliminated in the United States, providing a model for controlling emerging zoonoses (15,16).

Tobacco Control

Since publication of the first Surgeon General's Report on tobacco in 1964, implementation of evidence-based policies and interventions by federal, state, and local public health authorities has reduced tobacco use significantly (17). By 2009, 20.6% of adults and 19.5% of youths were current smokers, compared with 23.5% of adults and 34.8% of youths 10 years earlier. However, progress in reducing smoking rates among youths and adults appears to have stalled in recent years. After a substantial decline from 1997 (36.4%) to 2003 (21.9%), smoking rates among high school students remained relatively unchanged from 2003 (21.9%) to 2009 (19.5%) (18). Similarly, adult smoking prevalence declined steadily from 1965 (42.4%) through the 1980s, but the rate of decline began to slow in the 1990s, and the prevalence remained relatively unchanged from 2004 (20.9%) to 2009 (20.6%) (19). Despite the progress that has been made, smoking still results in an economic burden, including medical costs and lost productivity, of approximately \$193 billion per year (20).

Although no state had a comprehensive smoke-free law (i.e., prohibit smoking in worksites, restaurants, and bars) in 2000, that number increased to 25 states and the District of Columbia (DC) by 2010, with 16 states enacting comprehensive smoke-free laws following the release of the 2006 Surgeon

General's Report (21). After 99 individual state cigarette excise tax increases, at an average increase of 55.5 cents per pack, the average state excise tax increased from 41.96 cents per pack in 2000 to \$1.44 per pack in 2010 (22). In 2009, the largest federal cigarette excise tax increase went into effect, bringing the combined federal and average state excise tax for cigarettes to \$2.21 per pack, an increase from \$0.76 in 2000. In 2009, the Food and Drug Administration (FDA) gained the authority to regulate tobacco products (23). By 2010, FDA had banned flavored cigarettes, established restrictions on youth access, and proposed larger, more effective graphic warning labels that are expected to lead to a significant increase in quit attempts (24).

Maternal and Infant Health

The past decade has seen significant reductions in the number of infants born with neural tube defects (NTDs) and expansion of screening of newborns for metabolic and other heritable disorders. Mandatory folic acid fortification of cereal grain products labeled as enriched in the United States beginning in 1998 contributed to a 36% reduction in NTDs from 1996 to 2006 and prevented an estimated 10,000 NTD-affected pregnancies in the past decade, resulting in a savings of \$4.7 billion in direct costs (25–27).

Improvements in technology and endorsement of a uniform newborn-screening panel of diseases have led to earlier life-saving treatment and intervention for at least 3,400 additional newborns each year with selected genetic and endocrine disorders (28,29). In 2003, all but four states were screening for only six of these disorders. By April 2011, all states reported screening for at least 26 disorders on an expanded and standardized uniform panel (29). Newborn screening for hearing loss increased from 46.5% in 1999 to 96.9% in 2008 (30). The percentage of infants not passing their hearing screening who were then diagnosed by an audiologist before age 3 months as either normal or having permanent hearing loss increased from 51.8% in 1999 to 68.1 in 2008 (30).

Motor Vehicle Safety

Motor vehicle crashes are among the top 10 causes of death for U.S. residents of all ages and the leading cause of death for persons aged 5–34 years (30). In terms of years of potential life lost before age 65, motor vehicle crashes ranked third in 2007, behind only cancer and heart disease, and account for an estimated \$99 billion in medical and lost work costs annually (31,32). Crash-related deaths and injuries largely are preventable. From 2000 to 2009, while the number of vehicle miles traveled on the nation's roads increased by 8.5%, the death rate related to motor vehicle travel declined from 14.9 per 100,000 population to 11.0, and the injury rate declined from 1,130 to

722; among children, the number of pedestrian deaths declined by 49%, from 475 to 244, and the number of bicyclist deaths declined by 58%, from 178 to 74 (33,34).

These successes largely resulted from safer vehicles, safer roadways, and safer road use. Behavior was improved by protective policies, including effective seat belt and child safety seat legislation; 49 states and the DC have enacted seat belt laws for adults, and all 50 states and DC have enacted legislation that protects children riding in vehicles (35). Graduated drivers licensing policies for teen drivers have helped reduce the number of teen crash deaths (36).

Cardiovascular Disease Prevention

Heart disease and stroke have been the first and third leading causes of death in the United States since 1921 and 1938, respectively (37,38). Preliminary data from 2009 indicate that stroke is now the fourth leading cause of death in the United States (39). During the past decade, the age-adjusted coronary heart disease and stroke death rates declined from 195 to 126 per 100,000 population and from 61.6 to 42.2 per 100,000 population, respectively, continuing a trend that started in the 1900s for stroke and in the 1960s for coronary heart disease (40). Factors contributing to these reductions include declines in the prevalence of cardiovascular risk factors such as uncontrolled hypertension, elevated cholesterol, and smoking, and improvements in treatments, medications, and quality of care (41–44).

Occupational Safety

Significant progress was made in improving working conditions and reducing the risk for workplace-associated injuries. For example, patient lifting has been a substantial cause of low back injuries among the 1.8 million U.S. health-care workers in nursing care and residential facilities. In the late 1990s, an evaluation of a best practices patient-handling program that included the use of mechanical patient-lifting equipment demonstrated reductions of 66% in the rates of workers' compensation injury claims and lost workdays and documented that the investment in lifting equipment can be recovered in less than 3 years (45). Following widespread dissemination and adoption of these best practices by the nursing home industry, Bureau of Labor Statistics data showed a 35% decline in low back injuries in residential and nursing care employees between 2003 and 2009.

The annual cost of farm-associated injuries among youth has been estimated at \$1 billion annually (46). A comprehensive childhood agricultural injury prevention initiative was established to address this problem. Among its interventions was the development by the National Children's Center for Rural Agricultural Health and Safety of guidelines for parents

to match chores with their child's development and physical capabilities. Follow-up data have demonstrated a 56% decline in youth farm injury rates from 1998 to 2009 (National Institute for Occupational Safety and Health, unpublished data, 2011).

In the mid-1990s, crab fishing in the Bering Sea was associated with a rate of 770 deaths per 100,000 full-time fishers (47). Most fatalities occurred when vessels overturned because of heavy loads. In 1999, the U.S. Coast Guard implemented Dockside Stability and Safety Checks to correct stability hazards. Since then, one vessel has been lost and the fatality rate among crab fishermen has declined to 260 deaths per 100,000 full-time fishers (47).

Cancer Prevention

Evidence-based screening recommendations have been established to reduce mortality from colorectal cancer and female breast and cervical cancer (48). Several interventions inspired by these recommendations have improved cancer screening rates. Through the collaborative efforts of federal, state, and local health agencies, professional clinician societies, not-for-profit organizations, and patient advocates, standards were developed that have significantly improved cancer screening test quality and use (49,50). The National Breast and Cervical Cancer Early Detection Program has reduced disparities by providing breast and cervical cancer screening services for uninsured women (49). The program's success has resulted from similar collaborative relationships. From 1998 to 2007, colorectal cancer death rates decreased from 25.6 per 100,000 population to 20.0 (2.8% per year) for men and from 18.0 per 100,000 to 14.2 (2.7% per year) for women (51). During this same period, smaller declines were noted for breast and cervical cancer death rates (2.2% per year and 2.4%, respectively) (52).

Childhood Lead Poisoning Prevention

In 2000, childhood lead poisoning remained a major environmental public health problem in the United States, affecting children from all geographic areas and social and economic levels. Black children and those living in poverty and in old, poorly maintained housing were disproportionately affected. In 1990, five states had comprehensive lead poisoning prevention laws; by 2010, 23 states had such laws. Enforcement of these statutes as well as federal laws that reduce hazards in the housing with the greatest risks has significantly reduced the prevalence of lead poisoning. Findings of the National Health and Nutrition Examination Surveys from 1976–1980 to 2003–2008 reveal a steep decline, from 88.2% to 0.9%, in the percentage of children aged 1–5 years with blood lead levels ≥ 10 $\mu\text{g}/\text{dL}$. The risks for elevated blood lead levels based on

socioeconomic status and race also were reduced significantly. The economic benefit of lowering lead levels among children by preventing lead exposure is estimated at \$213 billion per year (53).

Public Health Preparedness and Response

After the international and domestic terrorist actions of 2001 highlighted gaps in the nation's public health preparedness, tremendous improvements have been made. In the first half of the decade, efforts were focused primarily on expanding the capacity of the public health system to respond (e.g., purchasing supplies and equipment). In the second half of the decade, the focus shifted to improving the laboratory, epidemiology, surveillance, and response capabilities of the public health system. For example, from 2006 to 2010, the percentage of Laboratory Response Network labs that passed proficiency testing for bioterrorism threat agents increased from 87% to 95%. The percentage of state public health laboratories correctly subtyping *Escherichia coli* O157:H7 and submitting the results into a national reporting system increased from 46% to 69%, and the percentage of state public health agencies prepared to use Strategic National Stockpile material increased from 70% to 98% (54). During the 2009 H1N1 influenza pandemic, these improvements in the ability to develop and implement a coordinated public health response in an emergency facilitated the rapid detection and characterization of the outbreak, deployment of laboratory tests, distribution of personal protective equipment from the Strategic National Stockpile, development of a candidate vaccine virus, and widespread administration of the resulting vaccine. These public health interventions prevented an estimated 5–10 million cases, 30,000 hospitalizations, and 1,500 deaths (CDC, unpublished data, 2011).

Existing systems also have been adapted to respond to public health threats. During the 2009 H1N1 influenza pandemic, the Vaccines for Children program was adapted to enable provider ordering and distribution of the pandemic vaccine. Similarly, President's Emergency Plan for AIDS Relief clinics were used to rapidly deliver treatment following the 2010 cholera outbreak in Haiti.

Conclusion

From 1999 to 2009, the age-adjusted death rate in the United States declined from 881.9 per 100,000 population to 741.0, a record low and a continuation of a steady downward trend that began during the last century. Advances in public health contributed significantly to this decline; seven of the 10 achievements described in this report targeted one or more of the 15 leading causes of death. Related *Healthy People 2010* data are available at <http://www.cdc.gov/mmwr/preview/>

mmwrhtml/mm6019a5_addinfo.htm. The examples in this report also illustrate the effective application of core public health tools. Some, such as the establishment of surveillance systems, dissemination of guidelines, implementation of research findings, or development of effective public health programs, are classic tools by which public health has addressed the burden of disease for decades.

Although not new, the judicious use of the legal system, by encouraging healthy behavior through taxation or by shaping it altogether through regulatory action, has become an increasingly important tool in modern public health practice and played a major role in many of the achievements described in this report (55). The creative use of the whole spectrum of available options, as demonstrated here, has enabled public health practitioners to respond effectively. Public health practice will continue to evolve to meet the new and complex challenges that lie ahead.

Reported by

Domestic Public Health Achievements Team, CDC. Corresponding contributor: Ram Koppaka, MD, PhD, Epidemiology and Analysis Program Office, Office of Surveillance, Epidemiology, and Laboratory Services, CDC; rkoppaka@cdc.gov, 347-396-2847.

References

1. National Center for Health Statistics. Health, United States, 2010: with special feature on death and dying. Hyattsville, MD: CDC, National Center for Health Statistics, 2011. Available at <http://www.cdc.gov/nchs/hus.htm>. Accessed May 16, 2011.
2. Zhou F. Updated economic evaluation of the routine childhood immunization schedule in the United States. Presented at the 45th National Immunization Conference. Washington, DC; March 28–31, 2011.
3. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010; 201:32–41.
4. Tate JE, Cortese MM, Payne DC. Uptake, impact, and effectiveness of rotavirus vaccination in the United States: review of the first 3 years of postlicensure data. *Pediatr Infect Dis J* 2011;30(1 Suppl):S56–60.
5. Marin M, Zhang JX, Seward JF. Near elimination of varicella deaths in the US following implementation of the childhood vaccination program. *Pediatrics*. In press, 2011.
6. Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. *J Infect Dis* 2008;197:1282–8.
7. CDC. Vital signs: central line–associated blood stream infections—United States, 2001, 2008, and 2009. *MMWR* 2011;60:243–8.
8. CDC. Trends in tuberculosis—United States, 2010. *MMWR* 2011;60:333–7.
9. Ongoing multistate outbreak of *Escherichia coli* serotype O157:H7 infections associated with consumption of fresh spinach—United States, September 2006. *MMWR* 2006;55:1045–6.
10. CDC. Multistate outbreak of *Salmonella* serotype Tennessee infections associated with peanut butter—United States, 2006–2007. *MMWR* 2007;56:521–4.
11. Boxrud D, Monson T, Stiles T, Besser J. The role, challenges, and support of PulseNet laboratories in detecting foodborne disease outbreaks. *Public Health Rep* 2010;125(Suppl 2):57–62.
12. Gottlieb SL, Newbern EC, Griffin PM, et al. Multistate outbreak of listeriosis linked to turkey deli meat and subsequent changes in US regulatory policy. *Clin Infect Dis* 2006;42:29–36.
13. CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR* 2006;55(No. RR-14).
14. Pealer LN, Marfin AA, Petersen LR, et al. Transmission of West Nile virus through blood transfusion in the United States in 2002. *N Engl J Med* 2003;349:1236–45.
15. Blanton JD, Hanlon CA, Rupprecht CE. Rabies surveillance in the United States during 2006. *J Am Vet Med Assoc* 2007;231:540–56.
16. Rupprecht CE, Barrett J, Briggs D, et al. Can rabies be eradicated? *Dev Biol (Basel)* 2008;131:95–121.
17. US Department of Health, Education, and Welfare, Public Health Service. Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service. Washington, DC: US Department of Health Education and Welfare, Public Health Service; 1964.
18. CDC. Trends in the prevalence of tobacco use: national YRBS, 1991–2009. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at http://www.cdc.gov/healthyyouth/yrbs/pdf/us_tobacco_trend_yrbs.pdf. Accessed May 17, 2011.
19. CDC. Vital signs: current cigarette smoking among adults aged ≥18 years—United States, 2009. *MMWR* 2010;59:1135–40.
20. CDC. Smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 2000–2004. *MMWR* 2008;57:1226–8.
21. CDC. State smoke-free laws for worksites, restaurants, and bars—United States, 2000–2010. *MMWR* 2011;60:472–5.
22. CDC. State Tobacco Activities Tracking and Evaluation (STATE) System. Available at <http://www.cdc.gov/tobacco/statesystem>. Accessed May 17, 2011.
23. US Government Printing Office. Family Smoking Prevention and Tobacco Control Act. Public Law No. 111-31. Washington DC: US Government Printing Office; 2009. Available at <http://www.gpo.gov/fdsys/pkg/PLAW-111publ31/content-detail.html>. Accessed May 17, 2011.
24. CDC. CDC grand rounds: current opportunities in tobacco control. *MMWR* 2010;59:487–92.
25. CDC. Spina bifida and anencephaly before and after folic acid mandate—United States, 1995–1996 and 1999–2000. *MMWR* 2004;53:362–5.
26. CDC. CDC grand rounds: additional opportunities to prevent neural tube defects with folic acid fortification. *MMWR* 2010;59:980–4.
27. Grosse SD, Ouyang L, Collins JS, Green D, Dean JH, Stevenson RE. Economic evaluation of a neural tube defect recurrence-prevention program. *Am J Prevent Med* 2008;35:572–7.
28. CDC. Using tandem mass spectrometry for metabolic disease screening among newborns. A report of a work group. *MMWR* 2001;50(No. RR-3).
29. CDC. Impact of expanded newborn screening—United States, 2006. *MMWR* 2008;57:1012–5.
30. CDC. Summary of infants screened for hearing loss, diagnosed, and enrolled in early intervention, United States, 1999–2008. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at http://www.cdc.gov/ncbddd/hearingloss/2008-data/EHDI_1999_2008.pdf. Accessed May 17, 2011.
31. CDC. Web-based Injury Statistics Query and Reporting System (WISQARS). Available at <http://www.cdc.gov/injury/wisqars/index.html>. Accessed May 17, 2011.
32. Naumann RB, Dellinger AM, Zaloshnja E, Lawrence BA, Miller TR. Incidence and total lifetime costs of motor vehicle-related fatal and nonfatal injury by road user type, United States, 2005. *Traffic Inj Prev* 2010;11:353–60.
33. National Highway Traffic Safety Administration. Traffic safety facts, 2009 data: children. Washington, DC: US Department of Transportation; 2010. Report no. DOT HS 811-387.

Morbidity and Mortality Weekly Report

34. National Highway Traffic Safety Administration. Traffic safety facts 2009 (early edition). Washington, DC: US Department of Transportation; 2010. Report no. DOT HS 811-402.
35. Insurance Institute for Highway Safety. Child passenger safety. Arlington, VA: Insurance Institute for Highway Safety, Highway Loss Data Institute; 2011. Available at <http://www.iihs.org/laws/restraintoverview.aspx>. Accessed May 17, 2011.
36. Baker SP, Chen L-H, Li G. Nationwide review of graduated driver licensing. Washington, DC: AAA Foundation for Traffic Safety; 2007. Available at <http://www.aaafoundation.org/pdf/nationwidereviewofgdl.pdf>. Accessed May 17, 2011.
37. CDC. Leading causes of death 1900–1998. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics. Available at http://www.cdc.gov/nchs/data/dvs/lead1900_98.pdf. Accessed May 17, 2011.
38. Xu JQ, Kochanek KD, Murphy SL, Tejada-Vera B. Deaths: final data for 2007. Natl Vital Stat Rep 2010;58(19).
39. Kochanek KD, Xu JQ, Murphy SL, et al. Deaths: preliminary data for 2009. Natl Vital Stat Rep 2010;59(4).
40. CDC. Decline in deaths from heart disease and stroke—United States, 1900–1999. MMWR 1999;48:649–56.
41. Institute of Medicine. A population-based policy and systems change approach to prevent and control hypertension. Washington, DC: The National Academies Press; 2010.
42. CDC. Health, United States, 2009: with special feature on medical technology. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2010.
43. CDC. Use of a registry to improve acute stroke care—seven states, 2005–2009. MMWR 2011;60:206–10.
44. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 2011;123:e18–209.
45. Bureau of Labor Statistics. Table R6: incidence rates for nonfatal occupational injuries and illnesses involving days away from work per 10,000 full-time workers by industry and selected parts of body affected by injury or illness, 2003. Available at <http://www.bls.gov/iif/oshwc/osh/case/ostb1384.pdf>. Accessed May 17, 2011.
46. Zaloshnja E, Miller TR, Lee BC. Incidence and cost of nonfatal farm youth injury, United States, 2001–2006. J Agromedicine 2011;16:6–18.
47. CDC. Commercial fishing deaths—United States, 2000–2009. MMWR 2010;59:842–5.
48. CDC. The guide to community preventive services. Atlanta, GA: US Department of Health and Human Services, CDC; 2011. Available at <http://www.thecommunityguide.org/index.html>. Accessed May 17, 2011.
49. CDC. Breast cancer. Atlanta, GA: US Department of Health and Human Services, CDC; 2011. Available at <http://www.cdc.gov/cancer/breast>. Accessed May 17, 2011.
50. CDC. Colorectal cancer test use among persons aged ≥50 years—United States, 2001. MMWR 2003;52:193–6.
51. Kohler BA, Ward E, McCarthy BJ, et al. Annual report to the nation on the status of cancer, 1975–2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 2011;103:714–36.
52. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010;116:544–73.
53. Grosse SD, Matte TD, Schwartz J, et al. Economic gains resulting from the reduction in children's exposure to lead in the United States. Environ Health Perspect 2002;110:563–9.
54. CDC. Justification of estimates for appropriation committees. Fiscal year 2011. Atlanta, GA: US Department of Health and Human Services, CDC. Available at http://intra-apps.cdc.gov/fmo/appropriations_budget_formulation/appropriations_budget_form_pdf/fy2011_cdc_cj_final.pdf. Accessed May 17, 2011.
55. CDC. Law and public health at CDC. MMWR 2006;55(Suppl 2): 29–33.

Emergency Department Visits After Use of a Drug Sold as “Bath Salts” — Michigan, November 13, 2010–March 31, 2011

On May 18, this report was posted as an MMWR Early Release on the MMWR website (<http://www.cdc.gov/mmwr>).

On February 1, 2011, in response to multiple news reports, the Michigan Department of Community Health (MDCH) contacted the Children’s Hospital of Michigan Poison Control Center (PCC) regarding any reports of illness in the state caused by the use of recreational designer drugs sold as “bath salts.” Unlike traditional cosmetic bath salts, which are packaged and sold for adding to bath water for soaking and cleaning, the drugs sold as “bath salts” have no legitimate use for bathing and are intended for substance abuse. These products can contain stimulant compounds such as 3,4-methylenedioxypyrovalerone (MDPV) or 4-methylmethcathinone (mephedrone). The PCC told MDCH that, earlier in the day, the PCC had learned that numerous persons had visited the local emergency department (ED) in Marquette County with cardiovascular and neurologic signs of acute intoxication. This report summarizes the subsequent investigation, which identified 35 persons who had ingested, inhaled, or injected “bath salts” and visited a Michigan ED during November 13, 2010–March 31, 2011. Among the 35 patients, the most common signs and symptoms of toxicity were agitation (23 patients [66%]), tachycardia (22 [63%]), and delusions/hallucinations (14 [40%]). Seventeen patients were hospitalized, and one was dead upon arrival at the ED. The coordinated efforts of public health agencies, health-care providers, poison control centers, and law enforcement agencies enabled rapid identification of this emerging health problem. Mitigation of the problem required the execution of an emergency public health order to remove the toxic “bath salts” from the marketplace. Lessons from the Michigan experience could have relevance to other areas of the United States experiencing similar problems.

From November 2010 to January 2011, the Marquette County ED treated seven patients who arrived at the ED with hypertension, tachycardia, tremors, motor automatisms, mydriasis, delusions, and paranoia. Some patients were violent, placing increased demand on ED staff members. Responding to the cluster also placed additional demands on local law enforcement and foster care, because many patients had young children who needed care while their parents were incapacitated. The patients reported using “bath salts” purchased at a local store for about \$20 a package and labeled “not intended for human consumption.” By February 3, a total of 13 cases in Marquette County and one death had been reported to the PCC. Efforts by the local ED, law enforcement, and prosecuting attorney’s office led to the execution of an emergency

public health order on February 4 by the Marquette County Health Department. The proprietor of the store was ordered to immediately remove from sale and turn over to government authorities any and all products known as White Rush, Cloud Nine, Ivory Wave, Ocean Snow, Charge Plus, White Lightning, Scarface, Hurricane Charlie, Red Dove, White Dove, and Sextasy. The Michigan Department of State Police laboratory tested the White Rush seized from the store and detected the presence of MDPV.

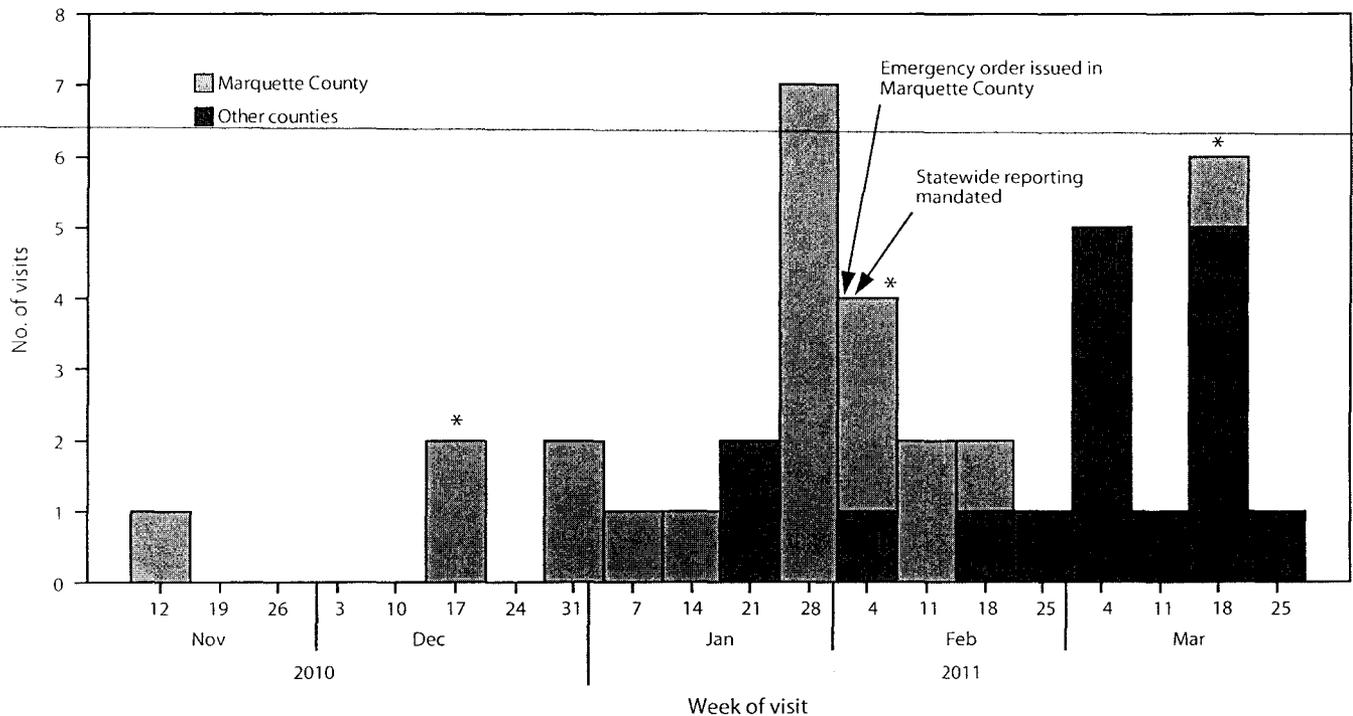
Concurrently, the PCC became aware of two cases elsewhere in the state. On February 5, MDCH used its chemical poisoning regulations to mandate statewide reporting by hospitals of cases of possible “bath salts” intoxication so that cases could be identified and characterized. Health-care providers were notified via the Michigan Health Alert Network about new cases and the potential for severe physical and psychological effects of “bath salts” abuse, and were provided a standardized reporting form. The PCC was designated as an agent of the state so it could receive case reports directly, allowing for mandatory reporting 24 hours a day, 7 days a week. As part of the investigation, patient information for Marquette County cases occurring before mandatory reporting was abstracted from medical charts by a MDCH staff member. A case was defined in a person who visited a Michigan ED during November 13, 2010–March 31, 2011, after self-reported or suspected use of “bath salts” (traditional cosmetic bath salts were excluded), with cardiovascular, neurologic, or psychological signs or symptoms consistent with acute intoxication.

Overall, the investigation identified 35 patients in Michigan, including three who visited the ED twice for “bath salt” abuse (Figure). The patients were aged 20–55 years (median: 28 years) (Table). Nineteen (54%) were men, and 16 (46%) were women. Twenty-four persons (69%) had a self-reported history of drug abuse, with 11 (31%) reporting polysubstance abuse and 12 (34%) intravenous drug abuse. Sixteen persons (46%) had a history of mental illness (e.g., bipolar disorder, schizophrenia, or depression) in their medical records, and six had suicidal thoughts or suspected attempts that might have been related to “bath salts” abuse. Twenty-seven cases (77%) occurred in Michigan’s Upper Peninsula region, with 18 cases (51%) occurring in Marquette County. Ten (12%) of Michigan’s 83 counties reported cases.

Clinical findings were consistent with intoxication with stimulants. Of the 35 patients, 32 (91%) had neurologic, 27 (77%) had cardiovascular, and 17 (49%) had psychological symptoms. Seventeen patients were hospitalized, 15 were

Morbidity and Mortality Weekly Report

FIGURE. Number of patient visits to emergency departments (N = 38) after exposure to drugs sold as "bath salts," by county and week of visit — Michigan, November 13, 2010–March 31, 2011



* Second emergency department visit by patient.

treated and released from the ED, two left the ED against medical advice, and one was dead on arrival at the ED. Twenty-two of the patients (63%) had injected the drug, nine (26%) had snorted it, and four (11%) had ingested it. For five patients (14%), including the patient who died, the exposure route was unknown, and five patients had more than one exposure route (Table). No relationship was found between the exposure route and severity of illness. Of the 17 patients with known drug test results, 16 (94%) tested positive for other drugs (e.g., marijuana, opiates, benzodiazepines, cocaine, or amphetamines). Toxicology results for the person who died revealed a high level of MDPV, along with marijuana and prescription drugs. Autopsy results revealed MDPV toxicity to be the primary factor contributing to death. The manner of death was ruled accidental, consistent with an attempt to get high.

Of the 17 hospitalized persons, nine were admitted to the intensive care unit (ICU), five were admitted to a general floor, and three were admitted directly to a psychiatric unit. Four persons who were first hospitalized in the ICU or a general floor later were transferred to a psychiatric unit. Treatment generally included a benzodiazepine such as lorazepam to control signs of toxicity; low or moderate doses usually were sufficient. Antipsychotics were used as secondary agents when benzodiazepine sedation was ineffective.

Of three patients who revisited the ED, one had rhabdomyolysis, chest pain, and dizziness but left against medical advice. Two months later, the patient was admitted to the ICU, moved to a psychiatric floor for 12 days, and then transferred to a different hospital for liver failure. The second patient was admitted to the hospital, discharged, and revisited the ED the same day of discharge after again using "bath salts." The third patient was treated in the ED twice, with the visits 1 month apart.

The investigation by MDCH and the PCC is continuing. As of May 16, 2011, a total of 71 emergency department visits by 65 patients who had used "bath salts" had been reported in Michigan since November 13, 2010.

Reported by

Fred Benzie, MPH, MPA, Marquette County Health Dept; Kimberly Hekman, MPH, CDC/ICSTE Applied Epidemiology Fellow, Lorraine Cameron, PhD, David R. Wade, PhD, Corinne Miller, PhD, Michigan Dept of Community Health; Susan Smolinske, PharmD, Brandon Warrick, MD, Children's Hospital of Michigan Poison Control Center. **Corresponding contributor:** Kimberly Hekman, Michigan Dept of Community Health, hekmank@michigan.gov, 517-373-2682.

Morbidity and Mortality Weekly Report

TABLE. Demographic and clinical characteristics for 35 patients evaluated in emergency departments (EDs) after exposure to drugs sold as “bath salts” — Michigan, November 13, 2010–March 31, 2011

Characteristic	No.	(%)
Sex		
Women	16	(46)
Men	19	(54)
Age group (yrs)		
20–29	22	(63)
30–39	5	(14)
40–49	6	(17)
≥50	2	(6)
Exposure route*		
Injected	22	(63)
Snorted	9	(26)
Ingested	4	(11)
Unknown	5	(14)
Additional drug use†		
Marijuana	10	(29)
Opiates	8	(23)
Benzodiazepines	5	(14)
Cocaine	4	(11)
Amphetamines	2	(6)
Signs and symptoms		
Agitation	23	(66)
Tachycardia	22	(63)
Delusions/hallucinations	14	(40)
Seizure/tremor	10	(29)
Hypertension	8	(23)
Drowsiness	8	(23)
Paranoia	7	(20)
Mydriasis	7	(20)
Disposition‡		
Treated in ED and released	15	(43)
Admitted	17	(49)
Dead upon arrival	1	(3)
Left against medical advice	2	(6)

* Five patients reported two exposure routes.

† Seventeen patients had known drug test results.

‡ Most severe disposition was chosen for three patients who revisited the ED.

Editorial Note

Through March 22, 2011, poison control centers representing 45 states and the District of Columbia had reported receiving telephone calls related to “bath salts” in 2011 (1). By April 6, centers had already received five times more “bath salts” calls in 2011 than in 2010 (2). Although “bath salt” abuse has been documented nationwide, this report is the first to summarize the epidemiology of a number of ED cases. Of note in this investigation, nearly half the patients had a history of serious mental illness (e.g., bipolar disorder, schizophrenia, or depression) in their medical records, and 16 of 17 patients with known drug test results tested positive for drugs other than those in the “bath salts.”

Drug overdose, including from designer drugs, continues to grow as a public health concern. Multistate investigations have been conducted as a result of exposure to nonpharmaceutical fentanyl (3), levamisole-contaminated cocaine (4), and opiates

What is already known on this topic?

Designer drugs sold as “bath salts” are available at “head shops,” convenience stores, gas stations, and on the Internet for recreational drug use.

What is added by this report?

This report is the first public health investigation of emergency department (ED) cases resulting from the use of “bath salts.” A total of 35 patients were identified at Michigan EDs during November 13, 2010–March 31, 2011; 17 patients were hospitalized, and one died.

What are the implications for public health practice?

Coordination between public health departments, poison control centers, health-care providers, and law enforcement is important for timely detection that will prevent further drug-related morbidity and mortality.

(5,6). Classes of designer drugs like “bath salts” are intended to have pharmacologic effects similar to controlled substances but to be chemically distinct from them, thus avoiding legal control. “Bath salts” for recreational use are sold at “head shops” and on the Internet with names such as Zoom and White Rush. These products also have been labeled as “plant food” and “pond water cleaner” and sold in ways to circumvent detection or enforcement. Some products are labeled as “novelty collector’s items,” despite additional, pharmaceutical-like labels that indicate dosage. Before “bath salts,” synthetic marijuana (e.g., K2 or Spice) was sold legally in convenience stores and gas stations as “incense.”

Designer drugs present an enforcement dilemma. Although MDPV and other chemical constituents of “bath salts” are not listed on state and federal controlled substances schedules, they could be included because of their structural similarity to scheduled chemicals under the analogue provisions of those laws. However, inclusion is problematic because the structure of MDPV is similar to that of medications used to treat conditions such as depression and anaphylaxis. Furthermore, laws also require that scheduled substances be intended for consumption. “Bath salts” typically are labeled “not for human consumption,” and thus fail to meet all attributes of a scheduled substance. Therefore, Michigan and other states have pursued legislation to add these chemicals to the state’s Schedule I list of controlled substances.

Michigan’s investigation involved collaborators from public health, law enforcement, and health care. An emergency order issued by the Marquette County Health Department was effective at stemming “bath salts” abuse locally, and statewide mandated reporting helped detect cases in other counties. These methods might be useful to other jurisdictions where emergent problems need to be addressed quickly. Poison control centers and emergency departments can act as sentinels

Morbidity and Mortality Weekly Report

for discovering new drugs of abuse. Drug treatment programs also might be effective as warning networks. The PCC was designated as an agent of the state to receive mandated reports supporting joint reporting and provision of medical toxicologic consultation. Planning among collaborating agencies is critical to implementing appropriate strategies to reduce drug-related morbidity and mortality.

Acknowledgments

The findings in this report are based, in part, on contributions by S Schreiber, MPH, Michigan Dept of Community Health; S Emerson, MD, L Wallace, Marquette General Health System, K Piggott, MD, Marquette General Health System and Marquette County Health Dept; Michigan Dept of State Police Forensic Science Div; and Michigan Dept of Community Health Bureau of Substance Abuse and Addiction Svcs.

References

1. American Association of Poison Control Centers. U.S. poison centers raise alarm about toxic substance marketed as bath salts; states begin taking action. Alexandria, VA: American Association of Poison Control Centers; March 22, 2011. Available at <http://www.aapcc.org/dnn/portals/0/prrel/bathsaltsmarch22.pdf>. Accessed May 17, 2011.
2. American Association of Poison Control Centers. U.S. poison centers raise alarm about toxic substance marketed as bath salts; states begin taking action. Alexandria, VA: American Association of Poison Control Centers; April 6, 2011. Available at <http://www.aapcc.org/dnn/portals/0/prrel/april6bathsalts.pdf>. Accessed May 17, 2011.
3. CDC. Nonpharmaceutical fentanyl-related deaths—multiple states, April 2005–March 2007. *MMWR* 2008;57:793–6.
4. CDC. Agranulocytosis associated with cocaine use—four states, March 2008–November 2009. *MMWR* 2009;58:1381–5.
5. Paulozzi LJ. Opioid analgesic involvement in drug abuse deaths in American metropolitan areas. *Am J Public Health* 2006;96:1755–7.
6. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. *Addiction* 2009;104:1541–8.

Notes from the Field

Update on Human *Salmonella* Typhimurium Infections Associated with Aquatic Frogs — United States, 2009–2011

CDC is collaborating with state and local public health departments in an ongoing investigation of human *Salmonella* Typhimurium infections associated with African dwarf frogs (ADFs) (1). ADFs are aquatic frogs of the genus *Hymenochirus* commonly kept in home aquariums as pets. From April 1, 2009 to May 10, 2011, a total of 224 human infections with a unique strain of *S. Typhimurium* were reported from 42 states. The isolates are indistinguishable by pulsed-field gel electrophoresis and multiple-locus variable-number tandem repeat analysis. This outbreak likely includes considerably more than the 224 laboratory-confirmed cases reported to CDC; only an estimated 3% of *Salmonella* infections are laboratory confirmed and reported to surveillance systems (2). Surveillance for additional cases continues through PulseNet, the national molecular subtyping network for foodborne disease surveillance.

The median age of patients in this outbreak was 5 years (range: <1–67 years), and 70% (156 of 223) were aged <10 years. Approximately 52% (111 of 215) were female. No deaths have been reported, but 30% (37 of 123) of patients were hospitalized. Sixty-five percent (56 of 86) of patients interviewed reported contact with frogs in the week before illness; 82% (45 of 55) reported that this contact took place in the home. Of those who could recall the type of frog, 85% (29 of 34) identified ADFs. Median time from acquiring a frog to illness onset was 15 days (range: 7–240 days).

Samples collected during 2009–2011 from aquariums housing ADFs in six homes of patients yielded the *S. Typhimurium* outbreak strain. Traceback investigations conducted during 2009–2011 from 21 patient homes and two ADF distributors identified a breeder in California as the common source of ADFs. This breeder sells ADFs to distributors, not directly

to pet stores or to the public. Environmental samples collected at the breeding facility in January 2010, April 2010, and March 2011 yielded the outbreak strain. Based on these epidemiologic, traceback, and laboratory findings, the breeder voluntarily suspended distribution of ADFs on April 19, 2011. Public health officials are working with the breeder to implement control measures.

Distribution of ADFs currently is unregulated by federal or state agencies. To prevent infection, the public needs to be aware of the risk of *Salmonella* infections associated with keeping amphibians, including frogs, as pets. Education of consumers, health-care professionals, and the pet industry is needed. Persons at high-risk for *Salmonella* infections, especially children <5 years, pregnant women, and immunocompromised persons, should avoid contact with frogs, water used by the frogs, and their habitats. Additional information is available at <http://www.cdc.gov/salmonella/water-frogs-0411>.

Reported by

Jill Yaeger, Phil Hudecek, Madera County Dept of Environmental Health. Curtis L. Fritz, Debra Gilliss, Duc J. Vugia, Gregory Inami, Rita A. Brenden, California Dept of Public Health. Jennifer K. Adams, Cheryl A. Bopp, Eija Trees, Vincent Hill, Amy Kahler, Jeshua Pringle, Ian Williams, Casey Barton Behraves, Div of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases; Sarah D. Bennett, Shauna L. Mettee, EIS officers, CDC. **Corresponding contributor:** Sarah D. Bennett, sbennett@cdc.gov, 404-639-2274.

References

1. CDC. Multistate outbreak of human *Salmonella* Typhimurium infections associated with aquatic frogs—United States, 2009. MMWR 2010;58:1433–6.
2. Voetsch AC, Van Gilder TJ, Angulo FJ, et al. FoodNet estimate of the burden of illness caused by nontyphoidal *Salmonella* infections in the United States. Clin Infect Dis 2004;38:S127–34.

Announcements

Click It or Ticket Campaign — May 23–June 5, 2011

In 2009, motor vehicle crashes resulted in approximately 23,000 deaths to passenger vehicle occupants (excluding motorcyclists), and 2.6 million occupants were treated for injuries in emergency departments in the United States (1,2). Although seat belt use in the United States is now estimated at 85%, millions of persons continue to travel unrestrained (3). Using a seat belt is one of the most effective means of preventing serious injury or death in the event of a crash. Seat belts saved an estimated 12,713 lives in 2009, but almost 4,000 additional lives could have been saved if every occupant had been buckled up (4).

Click It or Ticket, a national campaign coordinated annually by the National Highway Traffic Safety Administration (NHTSA) to increase the proper use of seat belts, takes place May 23–June 5, 2011. Law enforcement agencies across the nation will participate by conducting intensive, high-visibility enforcement of seat belt laws. Campaign activities will focus on young adult men (aged 18–34 years) and on nighttime travel. Additional information regarding Click It or Ticket activities is available from NHTSA at <http://www.nhtsa.gov>. Additional information on preventing motor vehicle crash injuries is available from CDC at <http://www.cdc.gov/motorvehiclesafety>.

References

1. National Highway Traffic Safety Administration. Traffic safety facts 2009: early edition. Washington, DC: US Department of Transportation; 2010. DOT-HS-811-402. Available at <http://www-nrd.nhtsa.dot.gov/pubs/811402ee.pdf>. Accessed May 12, 2011.
2. CDC. WISQARS (Web-based Injury Statistics Query and Reporting System). Available at <http://www.cdc.gov/injury/wisqars>. Accessed May 12, 2011.
3. Beck LF, West BA. Nonfatal, motor vehicle–occupant injuries (2009) and seat belt use (2008) among adults—United States. *MMWR* 2011;59:1681–6.
4. National Highway Traffic Safety Administration. Lives saved in 2009 by restraint use and minimum-drinking-age laws. Washington, DC: US Department of Transportation; 2010. DOT-HS-811-383. Available at <http://www-nrd.nhtsa.dot.gov/Pubs/811383.pdf>. Accessed May 12, 2011.

ATSDR Health Survey of Pre-1986 Personnel at Camp Lejeune

During June–December 2011, the Agency for Toxic Substances and Disease Registry will conduct a health survey of persons who resided or worked at Marine Corps Base Camp Lejeune in North Carolina before 1986 and might have been exposed to contaminated drinking water. The purpose of the survey is to learn more about participants' health. Health surveys also will be mailed to a comparison group of former active duty marines, sailors, and civilian employees, sampled from those who lived or worked at Marine Corps Base Camp Pendleton in California.

Eligible participants who were formerly at Camp Lejeune include 1) former active duty marines and sailors who were stationed at Camp Lejeune any time during June 1975–December 1985, 2) civilian employees who worked at Camp Lejeune any time during December 1972–December 1985, 3) families who took part in the 1999–2002 ATSDR telephone survey of childhood cancers and birth defects, and 4) persons who registered with the Camp Lejeune notification registry.

Participants will receive a paper copy of the health survey and instructions for completing and mailing. A web-based version of the survey also will be available for those who prefer to answer online. Health-care providers are asked to share information regarding the Camp Lejeune survey with their patients who lived or worked at the base before to 1986 and to encourage those receiving a health survey for either Camp Lejeune or Camp Pendleton to fill it out and return it or complete it online. Additional information is available at <http://www.atsdr.cdc.gov/sites/lejeune>.

Morbidity and Mortality Weekly Report

Notifiable Diseases and Mortality Tables

TABLE I. Provisional cases of infrequently reported notifiable diseases (<1,000 cases reported during the preceding year) — United States, week ending May 14, 2011 (19th week)*

Disease	Current week	Cum 2011	5-year weekly average†	Total cases reported for previous years					States reporting cases during current week (No.)
				2010	2009	2008	2007	2006	
Anthrax	—	—	—	—	—	—	—	—	
Arboviral diseases ^{§, ¶} :									
California serogroup virus disease	—	—	0	75	55	62	55	67	
Eastern equine encephalitis virus disease	—	—	—	10	4	4	4	8	
Powassan virus disease	—	—	0	8	6	2	7	1	
St. Louis encephalitis virus disease	—	—	0	10	12	13	9	10	
Western equine encephalitis virus disease	—	—	—	—	—	—	—	—	
Babesiosis	1	14	1	NN	NN	NN	NN	NN	NY (1)
Botulism, total	1	23	2	112	118	145	144	165	
foodborne	—	3	0	7	10	17	32	20	
infant	1	16	1	80	83	109	85	97	CA (1)
other (wound and unspecified)	—	4	1	25	25	19	27	48	
Brucellosis	3	16	3	117	115	80	131	121	PA (1), CA (2)
Chancroid	—	9	1	30	28	25	23	33	
Cholera	—	17	0	12	10	5	7	9	
Cyclosporiasis [§]	—	37	2	180	141	139	93	137	
Diphtheria	—	—	—	—	—	—	—	—	
<i>Haemophilus influenzae</i> , ** invasive disease (age <5 yrs):									
serotype b	—	1	0	23	35	30	22	29	
nonsertotype b	2	40	4	198	236	244	199	175	OH (1), NM (1)
unknown serotype	2	99	4	221	178	163	180	179	NE (1), FL (1)
Hansen disease [§]	3	19	1	71	103	80	101	66	FL (2), CA (1)
Hantavirus pulmonary syndrome [§]	—	6	1	19	20	18	32	40	
Hemolytic uremic syndrome, postdiarrheal [§]	—	25	4	256	242	330	292	288	
Influenza-associated pediatric mortality ^{§, ¶¶}	3	101	2	61	358	90	77	43	CO (1), NC (1), OK (1)
Listeriosis	4	143	11	816	851	759	808	884	PA (1), FL (2), WA (1)
Measles ^{§§}	19	80	3	61	71	140	43	55	PA (2), MN (17)
Meningococcal disease, invasive ^{¶¶} :									
A, C, Y, and W-135	—	68	6	276	301	330	325	318	
serogroup B	—	45	3	133	174	188	167	193	
other serogroup	—	4	1	11	23	38	35	32	
unknown serogroup	5	192	11	412	482	616	550	651	NE (2), FL (1), WA (2)
Novel influenza A virus infections ^{***}	—	1	0	4	43,774	2	4	NN	
Plague	—	—	0	2	8	3	7	17	
Poliomyelitis, paralytic	—	—	—	—	1	—	—	—	
Polio virus Infection, nonparalytic [§]	—	—	—	—	—	—	—	NN	
Psittacosis [§]	—	1	0	4	9	8	12	21	
Q fever, total [§]	—	22	3	132	113	120	171	169	
acute	—	12	2	108	93	106	—	—	
chronic	—	10	0	24	20	14	—	—	
Rabies, human	—	—	—	2	4	2	1	3	
Rubella ^{†††}	—	1	0	7	3	16	12	11	
Rubella, congenital syndrome	—	—	—	—	2	—	—	1	
SARS-CoV [§]	—	—	—	—	—	—	—	—	
Smallpox [§]	—	—	—	—	—	—	—	—	
Streptococcal toxic-shock syndrome [§]	—	49	4	179	161	157	132	125	
Syphilis, congenital (age <1 yr) ^{§§§}	—	49	6	333	423	431	430	349	
Tetanus	—	2	0	10	18	19	28	41	
Toxic-shock syndrome (staphylococcal) [§]	2	33	1	82	74	71	92	101	CA (2)
Trichinellosis	—	6	0	7	13	39	5	15	
Tularemia	1	10	2	125	93	123	137	95	MO (1)
Typhoid fever	4	117	7	466	397	449	434	353	OH (1), OK (1), WA (1), CA (1)
Vancomycin-intermediate <i>Staphylococcus aureus</i> [§]	1	20	1	91	78	63	37	6	NY (1)
Vancomycin-resistant <i>Staphylococcus aureus</i> [§]	—	—	—	2	1	—	2	1	
Vibriosis (noncholera <i>Vibrio</i> species infections) [§]	7	98	7	823	789	588	549	NN	OH (1), GA (1), FL (4), TN (1)
Viral hemorrhagic fever ^{§§§}	—	—	—	1	NN	NN	NN	NN	
Yellow fever	—	—	—	—	—	—	—	—	

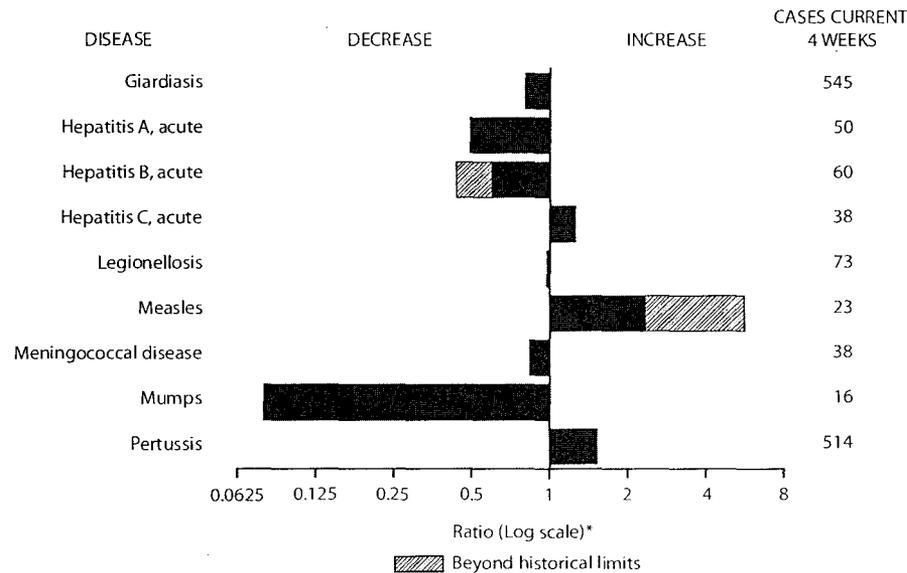
See Table 1 footnotes on next page.

Morbidity and Mortality Weekly Report

TABLE I. (Continued) Provisional cases of infrequently reported notifiable diseases (<1,000 cases reported during the preceding year) — United States, week ending May 14, 2011 (19th week)*

- : No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts.
- * Case counts for reporting years 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf.
- † Calculated by summing the incidence counts for the current week, the 2 weeks preceding the current week, and the 2 weeks following the current week, for a total of 5 preceding years. Additional information is available at http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/5yearweeklyaverage.pdf.
- ‡ Not reportable in all states. Data from states where the condition is not reportable are excluded from this table except starting in 2007 for the arboviral diseases, STD data, TB data, and influenza-associated pediatric mortality, and in 2003 for SARS-CoV. Reporting exceptions are available at http://www.cdc.gov/osels/ph_surveillance/nndss/phs/infdis.htm.
- § Includes both neuroinvasive and nonneuroinvasive. Updated weekly from reports to the Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ArboNET Surveillance). Data for West Nile virus are available in Table II.
- ** Data for H. influenzae (all ages, all serotypes) are available in Table II.
- †† Updated weekly from reports to the Influenza Division, National Center for Immunization and Respiratory Diseases. Since October 3, 2010, 105 influenza-associated pediatric deaths occurring during the 2010-11 influenza season have been reported.
- ‡‡ The nineteen measles cases reported for the current week were indigenous.
- §§ Data for meningococcal disease (all serogroups) are available in Table II.
- *** CDC discontinued reporting of individual confirmed and probable cases of 2009 pandemic influenza A (H1N1) virus infections on July 24, 2009. During 2009, four cases of human infection with novel influenza A viruses, different from the 2009 pandemic influenza A (H1N1) strain, were reported to CDC. The four cases of novel influenza A virus infection reported to CDC during 2010 and the one case reported in 2011 were identified as swine influenza A (H3N2) virus and are unrelated to the 2009 pandemic influenza A (H1N1) virus. Total case counts for 2009 were provided by the Influenza Division, National Center for Immunization and Respiratory Diseases (NCIRD).
- ††† No rubella cases were reported for the current week.
- §§§ Updated weekly from reports to the Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention.
- ¶¶¶ There was one case of viral hemorrhagic fever reported during week 12 of 2010. The one case report was confirmed as lassa fever. See Table II for dengue hemorrhagic fever.

FIGURE I. Selected notifiable disease reports, United States, comparison of provisional 4-week totals May 14, 2011, with historical data



* Ratio of current 4-week total to mean of 15 4-week totals (from previous, comparable, and subsequent 4-week periods for the past 5 years). The point where the hatched area begins is based on the mean and two standard deviations of these 4-week totals.

Notifiable Disease Data Team and 122 Cities Mortality Data Team

Willie J. Anderson
 Deborah A. Adams Rosaline Dhara
 Michael S. Wodajo Pearl C. Sharp
 Lenee Blanton

Morbidity and Mortality Weekly Report

TABLE II. Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	<i>Chlamydia trachomatis</i> infection					Coccidioidomycosis					Cryptosporidiosis				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	13,912	25,520	31,198	449,544	466,472	92	0	570	5,203	NN	60	122	370	1,355	2,085
New England	275	813	2,044	14,711	13,801	—	0	1	1	NN	—	6	19	71	188
Connecticut	191	166	1,558	2,620	3,152	N	0	0	N	NN	—	0	14	14	77
Maine†	—	55	100	1,092	921	N	0	0	N	NN	—	0	7	2	19
Massachusetts	—	406	860	7,795	7,341	N	0	0	N	NN	—	3	9	32	43
New Hampshire	3	53	112	1,029	675	—	0	1	1	NN	—	1	3	9	26
Rhode Island†	51	69	154	1,620	1,280	—	0	0	—	NN	—	0	2	1	7
Vermont†	30	26	84	555	432	N	0	0	N	NN	—	1	5	13	16
Mid. Atlantic	1,990	3,317	5,082	59,172	61,714	—	0	0	—	NN	11	14	38	208	218
New Jersey	251	501	684	7,684	9,655	N	0	0	N	NN	—	1	4	9	7
New York (Upstate)	756	707	2,098	12,998	11,622	N	0	0	N	NN	8	3	13	47	46
New York City	246	1,168	2,612	19,841	23,165	N	0	0	N	NN	—	2	6	21	20
Pennsylvania	737	954	1,183	18,649	17,272	N	0	0	N	NN	3	8	26	131	145
E.N. Central	1,108	3,977	7,039	64,979	73,655	—	0	3	15	NN	18	29	130	319	531
Illinois	—	1,136	1,320	12,201	21,835	N	0	0	N	NN	—	2	21	3	76
Indiana	253	444	3,376	10,486	5,588	N	0	0	N	NN	—	3	10	34	79
Michigan	526	939	1,400	17,491	19,068	—	0	3	8	NN	—	5	18	69	106
Ohio	167	1,000	1,136	17,009	18,914	—	0	3	7	NN	16	7	24	120	120
Wisconsin	162	452	551	7,792	8,250	N	0	0	N	NN	2	10	65	93	150
W.N. Central	350	1,412	1,592	24,524	26,796	—	0	0	—	NN	5	16	99	102	319
Iowa	21	203	240	3,691	4,052	N	0	0	N	NN	—	4	25	15	71
Kansas	—	190	287	3,317	3,626	N	0	0	N	NN	—	2	6	14	27
Minnesota	—	290	354	4,204	5,736	—	0	0	—	NN	—	3	22	—	106
Missouri	306	521	771	9,984	9,528	—	0	0	—	NN	1	3	29	35	47
Nebraska†	—	95	218	1,769	1,906	N	0	0	N	NN	4	3	26	31	35
North Dakota	—	41	91	332	799	N	0	0	N	NN	—	0	9	—	3
South Dakota	23	63	93	1,227	1,149	N	0	0	N	NN	—	1	6	7	30
S. Atlantic	3,705	5,017	6,195	93,319	93,741	—	0	1	1	NN	4	18	52	257	318
Delaware	122	83	220	1,672	1,589	—	0	0	—	NN	—	0	1	2	1
District of Columbia	63	106	180	1,803	1,938	—	0	0	—	NN	—	0	1	3	2
Florida	758	1,462	1,706	26,920	27,070	N	0	0	N	NN	2	6	19	75	128
Georgia	432	828	2,416	13,566	17,110	N	0	0	N	NN	2	5	11	84	103
Maryland†	399	496	1,125	7,831	8,149	—	0	1	1	NN	—	1	3	14	11
North Carolina	734	756	1,436	16,434	16,128	N	0	0	N	NN	—	0	16	23	24
South Carolina†	443	517	946	10,282	9,318	N	0	0	N	NN	—	2	8	31	17
Virginia†	684	658	970	13,255	11,067	N	0	0	N	NN	—	2	9	18	27
West Virginia	70	76	124	1,556	1,372	N	0	0	N	NN	—	0	5	7	5
E.S. Central	1,421	1,828	3,314	33,779	32,027	—	0	0	—	NN	1	4	19	47	68
Alabama†	192	554	1,552	9,985	8,661	N	0	0	N	NN	—	1	13	7	24
Kentucky	483	268	2,352	5,498	5,608	N	0	0	N	NN	—	1	6	16	23
Mississippi	422	394	780	7,585	8,181	N	0	0	N	NN	—	0	2	8	4
Tennessee†	324	588	795	10,711	9,577	N	0	0	N	NN	1	1	5	16	17
W.S. Central	2,291	3,307	4,723	57,923	65,779	—	0	1	1	NN	—	8	32	49	99
Arkansas†	328	304	440	5,987	5,686	N	0	0	N	NN	—	0	3	5	13
Louisiana	200	455	1,052	2,279	10,791	—	0	1	1	NN	—	1	6	10	14
Oklahoma	251	234	1,371	4,299	4,766	N	0	0	N	NN	—	1	8	—	14
Texas†	1,512	2,365	3,107	45,358	44,536	N	0	0	N	NN	—	4	24	34	58
Mountain	936	1,567	2,154	25,554	30,297	60	0	425	3,856	NN	18	10	30	145	173
Arizona	121	484	657	3,278	9,858	57	0	420	3,796	NN	1	1	3	10	13
Colorado	469	410	850	9,619	6,938	N	0	0	N	NN	10	2	6	45	47
Idaho†	—	66	199	1,019	1,359	N	0	0	N	NN	2	2	7	28	31
Montana†	—	64	83	1,192	1,132	N	0	0	N	NN	5	1	4	18	19
Nevada†	187	194	380	3,938	3,714	3	0	4	32	NN	—	0	7	2	5
New Mexico†	159	195	1,183	3,751	4,029	—	0	4	22	NN	—	2	12	27	29
Utah	—	128	175	2,110	2,489	—	0	2	3	NN	—	1	5	9	21
Wyoming†	—	39	90	647	778	—	0	2	3	NN	—	0	3	6	8
Pacific	1,836	3,814	6,572	75,583	68,662	32	0	145	1,329	NN	3	12	27	157	171
Alaska	—	116	157	2,033	2,282	N	0	0	N	NN	—	0	3	4	2
California	1,257	2,918	5,763	55,981	51,567	32	0	145	1,329	NN	2	7	19	90	97
Hawaii	—	108	158	1,633	2,323	N	0	0	N	NN	—	0	0	—	1
Oregon	258	229	496	4,998	4,541	N	0	0	N	NN	—	4	13	60	49
Washington	321	414	891	10,938	7,949	N	0	0	N	NN	1	1	9	3	22
Territories															
American Samoa	—	0	0	—	—	N	0	0	N	NN	N	0	0	N	NN
C.N.M.I.	—	—	—	—	—	—	—	—	—	NN	—	—	—	—	—
Guam	—	10	44	189	78	—	0	0	—	NN	—	0	0	—	—
Puerto Rico	—	104	251	1,933	2,284	N	0	0	N	NN	N	0	0	N	NN
U.S. Virgin Islands	—	14	29	220	191	—	0	0	—	NN	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

† Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	Dengue Virus Infection									
	Dengue Fever [†]				Dengue Hemorrhagic Fever [‡]					
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max			
United States	—	6	52	21	99	—	0	2	—	2
New England	—	0	3	—	3	—	0	0	—	—
Connecticut	—	0	0	—	—	—	0	0	—	—
Maine [§]	—	0	2	—	3	—	0	0	—	—
Massachusetts	—	0	0	—	—	—	0	0	—	—
New Hampshire	—	0	0	—	—	—	0	0	—	—
Rhode Island [¶]	—	0	1	—	—	—	0	0	—	—
Vermont [¶]	—	0	1	—	—	—	0	0	—	—
Mid. Atlantic	—	2	25	7	38	—	0	1	—	2
New Jersey	—	0	5	—	3	—	0	0	—	—
New York (Upstate)	—	0	5	—	5	—	0	1	—	1
New York City	—	1	17	—	24	—	0	1	—	1
Pennsylvania	—	0	3	7	6	—	0	0	—	—
E.N. Central	—	1	7	3	12	—	0	1	—	—
Illinois	—	0	3	1	4	—	0	0	—	—
Indiana	—	0	2	1	2	—	0	0	—	—
Michigan	—	0	2	—	1	—	0	0	—	—
Ohio	—	0	2	—	5	—	0	0	—	—
Wisconsin	—	0	2	1	—	—	0	1	—	—
W.N. Central	—	0	6	—	8	—	0	1	—	—
Iowa	—	0	1	—	—	—	0	0	—	—
Kansas	—	0	1	—	—	—	0	0	—	—
Minnesota	—	0	1	—	7	—	0	0	—	—
Missouri	—	0	0	—	—	—	0	0	—	—
Nebraska [¶]	—	0	6	—	—	—	0	0	—	—
North Dakota	—	0	0	—	1	—	0	0	—	—
South Dakota	—	0	0	—	—	—	0	1	—	—
S. Atlantic	—	2	19	6	26	—	0	1	—	—
Delaware	—	0	0	—	—	—	0	0	—	—
District of Columbia	—	0	0	—	—	—	0	0	—	—
Florida	—	2	14	5	23	—	0	1	—	—
Georgia	—	0	2	—	1	—	0	0	—	—
Maryland [¶]	—	0	0	—	—	—	0	0	—	—
North Carolina	—	0	2	1	—	—	0	0	—	—
South Carolina [¶]	—	0	3	—	—	—	0	0	—	—
Virginia [¶]	—	0	3	—	2	—	0	0	—	—
West Virginia	—	0	1	—	—	—	0	0	—	—
E.S. Central	—	0	2	—	—	—	0	0	—	—
Alabama [¶]	—	0	2	—	—	—	0	0	—	—
Kentucky	—	0	1	—	—	—	0	0	—	—
Mississippi	—	0	0	—	—	—	0	0	—	—
Tennessee [¶]	—	0	1	—	—	—	0	0	—	—
W.S. Central	—	0	1	—	—	—	0	1	—	—
Arkansas [¶]	—	0	0	—	—	—	0	1	—	—
Louisiana	—	0	0	—	—	—	0	0	—	—
Oklahoma	—	0	1	—	—	—	0	0	—	—
Texas [¶]	—	0	1	—	—	—	0	0	—	—
Mountain	—	0	2	1	3	—	0	0	—	—
Arizona	—	0	2	1	1	—	0	0	—	—
Colorado	—	0	0	—	—	—	0	0	—	—
Idaho [¶]	—	0	1	—	—	—	0	0	—	—
Montana [¶]	—	0	1	—	—	—	0	0	—	—
Nevada [¶]	—	0	1	—	1	—	0	0	—	—
New Mexico [¶]	—	0	0	—	1	—	0	0	—	—
Utah	—	0	0	—	—	—	0	0	—	—
Wyoming [¶]	—	0	0	—	—	—	0	0	—	—
Pacific	—	0	7	4	9	—	0	0	—	—
Alaska	—	0	0	—	1	—	0	0	—	—
California	—	0	5	1	5	—	0	0	—	—
Hawaii	—	0	0	—	—	—	0	0	—	—
Oregon	—	0	0	—	—	—	0	0	—	—
Washington	—	0	2	3	3	—	0	0	—	—
Territories										
American Samoa	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	104	550	191	1,911	—	2	20	1	49
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—

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[†] Dengue Fever includes cases that meet criteria for Dengue Fever with hemorrhage, other clinical and unknown case classifications.

[‡] DHF includes cases that meet criteria for dengue shock syndrome (DSS), a more severe form of DHF.

[¶] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	Ehrlichiosis/Anaplasmosis†														
	<i>Ehrlichia chaffeensis</i>					<i>Anaplasma phagocytophilum</i>					Undetermined				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	6	6	109	37	91	3	22	145	16	145	1	1	17	10	11
New England	—	0	2	—	2	—	1	9	1	16	—	0	1	—	—
Connecticut	—	0	0	—	—	—	0	6	—	5	—	0	0	—	—
Maine [§]	—	0	1	—	2	—	0	2	1	4	—	0	0	—	—
Massachusetts	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
New Hampshire	—	0	1	—	—	—	0	2	—	3	—	0	1	—	—
Rhode Island [§]	—	0	1	—	—	—	0	6	—	4	—	0	0	—	—
Vermont [§]	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Mid. Atlantic	—	1	8	4	20	1	5	17	4	13	—	0	2	1	1
New Jersey	—	0	6	—	15	—	1	7	—	11	—	0	1	—	—
New York (Upstate)	—	0	7	2	4	1	3	14	4	2	—	0	2	1	1
New York City	—	0	2	2	—	—	0	3	—	—	—	0	0	—	—
Pennsylvania	—	0	0	—	1	—	0	0	—	—	—	0	0	—	—
E.N. Central	—	0	4	2	9	—	5	45	1	54	—	1	6	3	6
Illinois	—	0	2	1	4	—	0	2	—	—	—	0	2	1	—
Indiana	—	0	0	—	—	—	0	0	—	—	—	0	3	1	5
Michigan	—	0	1	—	—	—	0	0	—	—	—	0	1	1	—
Ohio	—	0	3	1	—	—	0	1	—	—	—	0	0	—	—
Wisconsin	—	0	2	—	5	—	5	45	1	54	—	0	3	—	1
W.N. Central	5	1	13	9	11	—	4	77	1	55	1	0	15	3	—
Iowa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Kansas	—	0	2	1	—	—	0	1	—	—	—	0	0	—	—
Minnesota	—	0	12	—	—	—	4	75	1	55	—	0	15	—	—
Missouri	5	0	13	8	11	—	0	2	—	—	1	0	3	3	—
Nebraska [§]	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
North Dakota	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
South Dakota	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
S. Atlantic	1	3	18	19	39	1	1	7	7	6	—	0	1	—	—
Delaware	—	0	3	2	3	—	0	1	—	1	—	0	0	—	—
District of Columbia	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Florida	1	0	2	4	2	1	0	1	1	—	—	0	0	—	—
Georgia	—	0	2	1	8	—	0	1	1	—	—	0	1	—	—
Maryland [§]	—	0	3	2	4	—	0	2	—	3	—	0	1	—	—
North Carolina	—	1	13	6	18	—	0	4	5	1	—	0	0	—	—
South Carolina [§]	—	0	2	—	—	—	0	1	—	—	—	0	0	—	—
Virginia [§]	—	1	8	4	4	—	0	2	—	1	—	0	1	—	—
West Virginia	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
E.S. Central	—	0	11	3	7	1	0	2	2	1	—	0	2	1	2
Alabama [§]	—	0	3	—	1	—	0	2	1	—	—	0	0	—	—
Kentucky	—	0	2	1	—	—	0	0	—	—	—	0	0	—	—
Mississippi	—	0	1	—	—	—	0	1	—	—	—	0	1	—	—
Tennessee [§]	—	0	7	2	6	1	0	2	1	1	—	0	1	1	2
W.S. Central	—	0	87	—	2	—	0	9	—	—	—	0	1	—	—
Arkansas [§]	—	0	5	—	—	—	0	2	—	—	—	0	0	—	—
Louisiana	—	0	0	—	1	—	0	0	—	—	—	0	0	—	—
Oklahoma	—	0	82	—	—	—	0	7	—	—	—	0	0	—	—
Texas [§]	—	0	1	—	1	—	0	1	—	—	—	0	1	—	—
Mountain	—	0	0	—	—	—	0	0	—	—	—	0	1	2	—
Arizona	—	0	0	—	—	—	0	0	—	—	—	0	1	2	—
Colorado	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Idaho [§]	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Montana [§]	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Nevada [§]	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
New Mexico [§]	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Utah	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Wyoming [§]	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Pacific	—	0	1	—	1	—	0	0	—	—	—	0	0	—	2
Alaska	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
California	—	0	1	—	1	—	0	0	—	—	—	0	0	—	2
Hawaii	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Oregon	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Washington	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Territories	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationa%20NotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

† Cumulative total *E. ewingii* cases reported for year 2010 = 10, and 1 case reported for 2011.

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	Giardiasis					Gonorrhea					Haemophilus influenzae, invasive†				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	147	343	542	4,449	6,432	3,188	5,933	7,456	98,900	106,395	36	59	144	1,137	1,235
New England	4	25	55	294	538	70	100	206	1,693	1,819	—	3	9	59	74
Connecticut	—	4	12	—	106	68	38	150	680	860	—	0	6	—	12
Maine [§]	2	3	11	36	63	—	2	7	57	76	—	0	2	9	3
Massachusetts	—	14	25	176	225	—	49	80	778	717	—	2	6	37	43
New Hampshire	—	2	10	22	63	2	3	7	45	57	—	0	2	8	7
Rhode Island [§]	—	1	7	7	22	—	6	15	120	98	—	0	2	3	7
Vermont [§]	2	3	10	53	59	—	0	17	13	11	—	0	3	2	2
Mid. Atlantic	37	63	106	873	1,081	391	718	1,124	12,540	12,245	7	11	35	223	235
New Jersey	—	7	22	45	155	73	116	172	1,977	2,002	—	2	7	34	39
New York (Upstate)	20	22	72	316	363	112	110	271	1,965	1,812	5	3	18	60	61
New York City	7	17	30	269	304	49	236	497	4,119	4,292	1	2	5	41	43
Pennsylvania	10	15	27	243	259	157	264	366	4,479	4,139	1	4	11	88	92
E.N. Central	8	53	94	727	1,123	274	1,082	2,091	16,988	19,582	5	11	19	203	187
Illinois	—	10	32	121	259	—	301	369	3,046	5,269	—	3	9	55	58
Indiana	—	5	11	78	135	41	118	1,018	2,768	1,554	—	1	7	28	41
Michigan	1	11	25	161	241	139	250	489	4,401	5,222	1	1	4	28	15
Ohio	7	17	29	267	303	56	320	383	5,208	5,844	4	2	6	64	50
Wisconsin	—	9	35	100	185	38	97	152	1,565	1,693	—	2	5	28	23
W.N. Central	10	32	73	300	657	88	291	364	4,961	5,094	3	4	9	40	85
Iowa	4	5	12	73	92	4	35	57	659	631	—	0	0	—	1
Kansas	1	3	10	27	77	—	39	62	605	715	—	0	2	4	10
Minnesota	—	11	33	—	248	—	38	62	542	797	—	1	5	—	32
Missouri	3	8	26	118	121	83	143	181	2,566	2,357	1	1	5	19	32
Nebraska [§]	2	4	9	61	73	—	22	49	357	413	2	0	3	16	5
North Dakota	—	0	6	—	8	—	3	11	32	62	—	0	2	1	5
South Dakota	—	2	5	21	38	1	10	20	200	119	—	0	0	—	—
S. Atlantic	34	71	127	933	1,245	995	1,449	1,879	24,494	27,244	11	15	28	294	300
Delaware	—	0	5	7	10	16	17	48	348	369	—	0	1	1	3
District of Columbia	—	1	5	9	16	30	38	70	666	703	—	0	1	—	—
Florida	16	36	75	404	642	187	383	486	6,737	7,188	7	4	12	112	82
Georgia	10	14	51	318	258	155	277	891	3,985	5,558	—	3	7	58	69
Maryland [§]	4	4	11	70	121	81	134	246	1,989	2,281	2	1	5	23	20
North Carolina	N	0	0	N	N	221	267	596	5,533	5,072	2	2	9	35	39
South Carolina [§]	1	2	9	35	38	167	153	257	2,885	2,770	—	1	5	24	42
Virginia [§]	3	8	32	76	147	123	121	189	2,029	3,121	—	1	8	41	37
West Virginia	—	0	8	14	13	15	14	26	322	182	—	0	9	—	8
E.S. Central	3	4	11	50	98	400	495	1,007	8,888	8,516	3	3	10	72	74
Alabama [§]	3	4	11	48	55	60	161	404	2,990	2,531	—	1	4	24	8
Kentucky	N	0	0	N	N	133	72	712	1,433	1,391	—	1	4	12	13
Mississippi	N	0	0	N	N	129	115	216	1,979	2,226	—	0	2	5	6
Tennessee [§]	—	0	3	2	43	78	144	194	2,486	2,368	3	1	4	31	47
W.S. Central	1	5	14	64	126	549	871	1,664	14,514	17,588	2	3	26	58	59
Arkansas [§]	1	2	9	34	36	116	98	138	1,797	1,638	—	0	3	13	9
Louisiana	—	2	8	30	52	88	119	509	656	3,025	—	0	4	22	15
Oklahoma	—	0	5	—	38	54	80	332	1,234	1,348	2	1	19	22	31
Texas [§]	N	0	0	N	N	291	598	867	10,827	11,577	—	0	4	1	4
Mountain	13	30	58	368	599	105	183	229	2,888	3,369	5	5	12	118	152
Arizona	—	3	8	42	52	29	57	83	606	1,162	—	2	6	53	60
Colorado	9	12	27	172	256	35	49	93	825	959	2	1	5	24	38
Idaho [§]	1	4	9	45	81	—	2	14	42	37	2	0	2	6	7
Montana [§]	3	1	6	15	47	—	1	5	27	46	—	0	1	2	1
Nevada [§]	—	2	11	26	20	29	33	103	754	661	—	0	2	8	5
New Mexico [§]	—	2	6	17	29	12	27	98	550	364	1	1	4	19	20
Utah	—	5	13	40	94	—	4	10	66	128	—	0	3	6	16
Wyoming [§]	—	0	5	11	20	—	1	4	18	12	—	0	1	—	5
Pacific	37	51	129	840	965	316	657	808	11,934	10,938	—	3	10	70	69
Alaska	—	2	6	21	34	—	21	34	347	542	—	0	2	9	12
California	23	33	68	569	590	266	520	695	9,519	8,825	—	0	6	12	13
Hawaii	—	1	4	12	22	—	14	26	212	241	—	0	2	10	11
Oregon	3	8	20	147	183	9	22	41	442	383	—	1	6	38	29
Washington	11	9	57	91	136	41	61	115	1,414	947	—	0	2	1	4
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	1	—	1	—	0	5	6	5	—	0	0	—	—
Puerto Rico	—	0	8	8	29	—	6	12	129	99	—	0	0	—	1
U.S. Virgin Islands	—	0	0	—	—	—	3	7	44	34	—	0	0	—	—

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U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

† Data for H. influenzae (age <5 yrs for serotype b, nonserotype b, and unknown serotype) are available in Table I.

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	Hepatitis (viral, acute), by type														
	A					B					C				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	19	28	74	392	578	18	60	163	774	1,114	12	17	36	311	285
New England	—	1	6	12	49	—	0	3	16	28	—	1	4	17	23
Connecticut	—	0	4	5	11	—	0	3	3	8	—	0	4	11	11
Maine†	—	0	1	1	3	—	0	2	4	8	—	0	2	3	1
Massachusetts	—	0	5	3	30	—	0	3	8	7	—	0	1	1	11
New Hampshire	—	0	1	—	—	—	0	1	1	4	N	0	0	N	N
Rhode Island†	—	0	1	1	5	U	0	0	U	U	U	0	0	U	U
Vermont†	—	0	1	2	—	—	0	1	—	1	—	0	1	2	—
Mid. Atlantic	4	4	12	63	90	2	5	11	85	117	2	1	6	25	36
New Jersey	—	1	4	6	27	—	1	5	17	31	—	0	4	—	7
New York (Upstate)	3	1	4	17	18	2	1	9	17	17	1	1	4	15	15
New York City	—	1	6	22	26	—	1	4	21	36	—	0	1	—	1
Pennsylvania	1	1	3	18	19	—	1	3	30	33	1	0	2	10	13
E.N. Central	3	4	9	64	77	—	8	23	103	183	2	2	8	74	33
Illinois	—	1	3	10	24	—	2	7	23	41	—	0	1	1	—
Indiana	—	0	3	8	9	—	1	6	12	27	—	1	4	28	12
Michigan	1	1	5	23	24	—	2	5	33	51	2	1	6	42	16
Ohio	2	1	5	21	12	—	1	16	25	43	—	0	1	2	3
Wisconsin	—	0	2	2	8	—	1	3	10	21	—	0	1	1	2
W.N. Central	—	1	25	15	21	3	2	16	47	45	1	0	6	3	6
Iowa	—	0	3	1	4	—	0	1	4	9	—	0	0	—	—
Kansas	—	0	2	3	7	—	0	2	5	2	—	0	1	—	—
Minnesota	—	0	22	2	1	1	0	15	2	2	—	0	6	—	3
Missouri	—	0	1	4	7	2	1	3	29	24	—	0	1	—	2
Nebraska†	—	0	4	3	2	—	0	3	6	8	—	0	1	2	1
North Dakota	—	0	3	—	—	—	0	0	—	—	—	0	0	—	—
South Dakota	—	0	2	2	—	—	0	1	1	—	1	0	0	1	—
S. Atlantic	5	6	14	82	125	7	16	33	224	320	4	4	8	65	65
Delaware	—	0	1	1	5	—	0	2	—	14	U	0	0	U	U
District of Columbia	—	0	0	—	1	—	0	0	—	3	—	0	0	—	2
Florida	2	2	7	33	41	3	4	11	75	112	1	1	5	20	18
Georgia	3	1	4	22	14	3	2	8	37	65	1	0	3	11	8
Maryland†	—	0	2	8	11	—	1	4	20	28	—	0	3	11	9
North Carolina	—	0	4	7	23	1	2	16	54	27	2	1	4	18	16
South Carolina†	—	0	1	3	16	—	1	4	12	18	—	0	1	—	—
Virginia†	—	1	6	8	13	—	2	7	26	29	—	0	2	5	6
West Virginia	—	0	5	—	1	—	0	18	—	24	—	0	5	—	6
E.S. Central	—	0	6	7	17	1	8	14	141	107	1	3	8	50	50
Alabama†	—	0	2	—	4	—	1	4	33	23	—	0	1	3	1
Kentucky	—	0	6	2	9	—	3	8	43	35	—	2	6	23	35
Mississippi	—	0	1	2	1	—	1	3	10	10	U	0	0	U	U
Tennessee†	—	0	2	3	3	1	3	8	55	39	1	1	5	24	14
W.S. Central	2	2	15	26	49	2	9	63	82	162	2	2	11	36	23
Arkansas†	—	0	1	—	—	—	1	4	14	21	—	0	0	—	—
Louisiana	—	0	1	1	5	—	1	4	18	20	—	0	2	4	2
Oklahoma	—	0	4	1	—	—	2	14	16	21	1	1	10	19	9
Texas†	2	2	11	24	44	2	4	45	34	100	1	0	3	13	12
Mountain	5	2	8	27	64	1	2	7	28	47	—	1	4	15	24
Arizona	—	0	4	5	31	—	0	3	8	11	U	0	0	U	U
Colorado	1	0	2	8	14	1	0	5	3	13	—	0	3	1	7
Idaho†	1	0	2	4	3	—	0	1	2	3	—	0	2	6	6
Montana†	—	0	1	2	4	—	0	0	—	—	—	0	1	1	—
Nevada†	3	0	2	4	6	—	1	3	12	12	—	0	2	5	1
New Mexico†	—	0	1	3	3	—	0	2	2	2	—	0	1	2	7
Utah	—	0	2	—	3	—	0	1	1	6	—	0	2	—	3
Wyoming†	—	0	3	1	—	—	0	1	—	—	—	0	0	—	—
Pacific	—	6	15	96	86	2	5	25	48	105	—	1	9	26	25
Alaska	—	0	1	1	—	—	0	1	2	1	U	0	0	U	U
California	—	5	15	82	68	—	3	22	22	74	—	0	4	13	10
Hawaii	—	0	2	4	4	—	0	1	3	3	U	0	0	U	U
Oregon	—	0	1	2	8	1	1	3	14	17	—	0	3	7	8
Washington	—	0	2	7	6	1	1	4	7	10	—	0	5	6	7
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	5	8	10	—	1	8	28	18	—	0	7	10	19
Puerto Rico	—	0	2	2	7	—	0	2	1	10	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	Legionellosis					Lyme disease					Malaria				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	24	61	126	568	752	125	430	1,935	2,590	6,143	15	30	114	323	433
New England	—	4	16	26	43	3	107	503	258	1,986	—	1	20	13	27
Connecticut	—	0	6	—	9	—	34	213	—	804	—	0	20	—	—
Maine [†]	—	0	3	—	3	—	11	62	60	106	—	0	1	1	2
Massachusetts	—	2	10	17	23	—	24	223	94	673	—	0	4	9	20
New Hampshire	—	0	5	2	3	—	16	69	81	344	—	0	2	1	1
Rhode Island [†]	—	0	4	1	5	—	1	40	4	23	—	0	4	—	3
Vermont [†]	—	0	2	3	1	—	4	28	19	36	—	0	1	2	1
Mid. Atlantic	4	16	53	124	171	101	199	769	1,528	2,669	1	9	22	75	129
New Jersey	—	2	18	1	29	—	45	234	372	828	—	1	6	8	25
New York (Upstate)	2	5	19	56	45	23	36	159	245	352	—	1	6	11	23
New York City	—	2	17	23	37	—	9	31	2	174	1	5	13	44	60
Pennsylvania	2	5	19	44	60	78	91	386	909	1,315	—	1	3	12	21
E.N. Central	5	11	44	109	159	1	33	373	186	402	1	3	9	37	39
Illinois	—	2	15	12	22	—	1	18	4	11	—	1	6	12	19
Indiana	2	1	6	13	33	—	0	7	3	17	—	0	2	2	4
Michigan	—	2	20	23	27	—	1	14	4	4	—	0	4	7	4
Ohio	3	4	15	61	57	—	0	9	6	6	1	1	5	15	11
Wisconsin	—	0	5	—	20	1	29	345	169	364	—	0	2	1	1
W.N. Central	1	2	9	13	26	—	13	188	3	181	—	1	45	3	21
Iowa	—	0	2	2	2	—	0	10	1	10	—	0	2	—	6
Kansas	—	0	2	2	3	—	0	1	1	4	—	0	2	2	3
Minnesota	—	0	8	—	9	—	12	181	—	164	—	0	45	—	3
Missouri	1	0	4	8	5	—	0	1	—	—	—	0	3	—	3
Nebraska [†]	—	0	2	—	2	—	0	2	1	3	—	0	1	1	6
North Dakota	—	0	1	—	2	—	0	9	—	—	—	0	1	—	—
South Dakota	—	0	2	1	3	—	0	1	—	—	—	0	2	—	—
S. Atlantic	7	10	27	110	146	20	59	178	539	800	8	7	41	106	129
Delaware	—	0	3	2	5	7	10	33	155	202	—	0	1	2	2
District of Columbia	—	0	4	—	6	—	1	5	6	7	—	0	2	5	5
Florida	3	3	9	52	55	—	1	8	17	19	3	2	7	31	43
Georgia	—	1	4	3	22	—	0	2	1	3	2	1	7	20	20
Maryland [†]	3	2	6	19	29	8	19	104	202	374	2	1	21	21	21
North Carolina	1	1	7	17	12	—	1	9	13	29	—	0	13	9	18
South Carolina [†]	—	0	2	4	2	—	0	3	3	13	—	0	1	—	1
Virginia [†]	—	1	9	13	13	5	17	82	142	140	1	1	5	18	19
West Virginia	—	0	3	—	2	—	0	29	—	13	—	0	1	—	—
E.S. Central	2	2	10	28	30	—	0	4	8	13	—	0	3	7	6
Alabama [†]	1	0	2	6	3	—	0	2	4	—	—	0	1	2	1
Kentucky	—	0	4	5	8	—	0	1	—	1	—	0	1	3	2
Mississippi	—	0	3	3	2	—	0	0	—	—	—	0	2	1	—
Tennessee [†]	1	1	6	14	17	—	0	4	4	12	—	0	2	1	3
W.S. Central	—	3	13	20	27	—	1	29	11	26	—	1	18	15	24
Arkansas [†]	—	0	2	—	3	—	0	0	—	—	—	0	1	1	1
Louisiana	—	0	3	6	1	—	0	1	—	—	—	0	1	—	1
Oklahoma	—	0	3	1	—	—	0	0	—	—	—	0	1	2	2
Texas [†]	—	2	11	13	23	—	1	29	11	26	—	1	17	12	20
Mountain	2	2	10	27	53	—	0	3	3	3	1	1	4	16	19
Arizona	—	1	7	9	15	—	0	1	2	—	—	0	3	5	7
Colorado	1	0	2	3	13	—	0	1	—	—	1	0	3	5	6
Idaho [†]	—	0	1	1	—	—	0	2	—	1	—	0	1	1	—
Montana [†]	—	0	1	—	1	—	0	1	—	—	—	0	1	—	1
Nevada [†]	1	0	2	7	10	—	0	1	—	—	—	0	2	3	2
New Mexico [†]	—	0	2	2	2	—	0	2	1	1	—	0	1	2	—
Utah	—	0	2	4	10	—	0	1	—	1	—	0	0	—	3
Wyoming [†]	—	0	2	1	2	—	0	0	—	—	—	0	0	—	—
Pacific	3	5	21	111	97	—	4	11	54	63	4	4	10	51	39
Alaska	—	0	2	—	—	—	0	1	—	1	—	0	2	2	2
California	3	4	15	99	88	—	2	9	36	36	4	2	10	38	26
Hawaii	—	0	1	1	—	N	0	0	N	N	—	0	1	1	1
Oregon	—	0	3	3	2	—	0	3	18	25	—	0	3	5	4
Washington	—	0	6	8	7	—	0	4	—	1	—	0	5	5	6
Territories															
American Samoa	—	0	0	—	—	N	0	0	N	N	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	0	0	—	—	N	0	0	N	N	—	0	0	—	4
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

[†] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	Meningococcal disease, invasive†										Pertussis				
	All serogroups					Mumps					Pertussis				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	5	15	53	309	345	3	12	217	127	1,488	69	550	2,901	4,567	4,623
New England	—	0	4	17	6	—	0	2	1	16	—	10	24	111	106
Connecticut	—	0	1	1	—	—	0	0	—	11	—	1	8	—	17
Maine [§]	—	0	1	3	1	—	0	1	—	1	—	1	8	44	5
Massachusetts	—	0	2	9	2	—	0	2	1	4	—	5	13	48	74
New Hampshire	—	0	1	1	—	—	0	2	—	—	—	0	3	15	3
Rhode Island [§]	—	0	1	—	—	—	0	0	—	—	—	0	7	3	4
Vermont [§]	—	0	3	3	3	—	0	0	—	—	—	0	4	1	3
Mid. Atlantic	—	1	5	27	34	—	4	209	14	1,301	7	39	123	422	239
New Jersey	—	0	1	—	10	—	1	11	8	266	—	2	10	11	48
New York (Upstate)	—	0	4	7	6	—	0	7	2	624	2	12	81	133	82
New York City	—	0	3	11	9	—	0	201	4	397	—	0	12	7	3
Pennsylvania	—	0	2	9	9	—	0	16	—	14	5	20	70	271	106
E.N. Central	—	2	6	39	60	—	1	7	32	30	14	117	198	1,138	1,134
Illinois	—	0	3	11	10	—	1	3	19	10	—	22	52	191	192
Indiana	—	0	2	6	15	—	0	1	—	2	—	11	26	74	155
Michigan	—	0	4	5	8	—	0	1	5	11	4	31	57	393	336
Ohio	—	0	2	12	16	—	0	5	8	6	10	34	80	365	384
Wisconsin	—	0	2	5	11	—	0	1	—	1	—	13	26	115	67
W.N. Central	2	1	4	23	20	1	0	7	15	52	12	37	485	245	369
Iowa	—	0	1	6	5	—	0	7	3	16	—	11	36	52	136
Kansas	—	0	2	2	1	—	0	1	3	3	—	2	9	28	56
Minnesota	—	0	2	—	2	1	0	4	1	3	—	0	453	—	6
Missouri	—	0	2	8	8	—	0	3	6	8	5	7	43	109	128
Nebraska [§]	2	0	1	5	4	—	0	1	1	21	—	4	13	34	26
North Dakota	—	0	1	1	—	—	0	1	1	—	7	0	30	20	—
South Dakota	—	0	1	1	—	—	0	1	—	1	—	0	2	2	17
S. Atlantic	1	2	7	55	67	1	0	4	10	31	5	38	106	467	455
Delaware	—	0	1	1	—	—	0	0	—	—	—	0	4	6	—
District of Columbia	—	0	1	—	—	—	0	1	—	2	—	0	2	2	3
Florida	1	1	5	24	35	—	0	2	2	6	3	6	28	103	78
Georgia	—	0	2	3	5	—	0	2	1	1	1	4	13	69	69
Maryland [§]	—	0	1	5	2	1	0	1	1	7	—	2	6	36	46
North Carolina	—	0	3	10	8	—	0	2	4	5	1	3	35	93	129
South Carolina [§]	—	0	1	4	5	—	0	1	—	3	—	6	25	52	75
Virginia [§]	—	0	2	8	11	—	0	2	2	5	—	7	41	106	48
West Virginia	—	0	1	—	1	—	0	0	—	2	—	0	41	—	7
E.S. Central	—	1	3	13	17	—	0	2	3	6	2	12	35	132	302
Alabama [§]	—	0	1	6	4	—	0	2	1	4	1	3	8	42	81
Kentucky	—	0	2	—	6	—	0	1	—	—	—	3	16	39	115
Mississippi	—	0	1	2	2	—	0	1	2	—	—	1	10	5	21
Tennessee [§]	—	0	2	5	5	—	0	1	—	2	1	3	11	46	85
W.S. Central	—	1	12	26	41	1	2	15	39	27	18	51	295	354	1,039
Arkansas [§]	—	0	1	6	5	—	0	1	—	1	2	2	18	18	55
Louisiana	—	0	1	5	11	—	0	2	—	2	—	1	3	10	13
Oklahoma	—	0	2	4	12	—	0	1	1	—	—	1	92	17	5
Texas [§]	—	1	10	11	13	1	2	14	38	24	16	42	187	309	966
Mountain	—	1	6	24	24	—	0	4	1	7	6	43	100	744	403
Arizona	—	0	2	7	7	—	0	1	—	2	—	12	29	273	157
Colorado	—	0	4	2	6	—	0	1	—	5	4	13	63	284	45
Idaho [§]	—	0	1	3	3	—	0	1	—	—	—	2	15	32	50
Montana [§]	—	0	2	3	1	—	0	0	—	—	—	2	16	51	7
Nevada [§]	—	0	1	3	4	—	0	1	—	—	2	0	7	10	3
New Mexico [§]	—	0	1	1	2	—	0	2	1	—	—	2	11	44	32
Utah	—	0	1	5	1	—	0	1	—	—	—	6	16	48	105
Wyoming [§]	—	0	1	—	—	—	0	1	—	—	—	0	2	2	4
Pacific	2	4	26	85	76	—	0	5	12	18	5	146	1,710	954	576
Alaska	—	0	1	1	—	—	0	1	1	1	—	0	6	14	11
California	—	2	17	59	49	—	0	4	6	13	—	128	1,569	749	403
Hawaii	—	0	1	3	1	—	0	1	2	1	—	1	6	14	21
Oregon	—	1	3	15	13	—	0	1	3	1	1	5	12	80	90
Washington	2	0	8	7	13	—	0	2	—	2	4	9	131	97	51
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	1	7	14	35	—	0	14	31	—
Puerto Rico	—	0	0	—	—	—	0	1	—	—	—	0	1	1	1
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

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† Data for meningococcal disease, invasive caused by serogroups A, C, Y, and W-135; serogroup B; other serogroup; and unknown serogroup are available in Table I.

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	Rabies, animal				Salmonellosis				Shiga toxin-producing <i>E. coli</i> (STEC) [†]						
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	48	51	144	637	1,221	452	965	1,815	8,966	11,267	46	102	257	1,016	1,049
New England	4	4	18	32	103	1	30	144	420	979	—	2	13	29	93
Connecticut	—	0	14	—	54	—	0	122	122	491	—	0	12	12	60
Maine [§]	2	1	3	15	23	1	3	8	41	27	—	0	3	3	3
Massachusetts	—	0	0	—	—	—	19	52	204	351	—	1	9	5	20
New Hampshire	—	0	6	4	4	—	3	12	30	55	—	0	3	7	8
Rhode Island [§]	—	0	4	2	4	—	2	17	10	39	—	0	1	—	—
Vermont [§]	2	1	3	11	18	—	1	5	13	16	—	0	2	2	2
Mid. Atlantic	3	16	33	92	397	41	97	218	978	1,372	2	10	30	105	111
New Jersey	—	0	0	—	—	—	22	57	73	255	—	2	9	11	26
New York (Upstate)	3	8	19	92	160	21	26	63	278	318	2	4	12	37	34
New York City	—	0	4	—	115	2	22	53	250	327	—	1	6	16	10
Pennsylvania	—	6	17	—	122	18	29	81	377	472	—	3	13	41	41
E.N. Central	2	2	27	21	30	28	90	265	949	1,458	7	11	48	135	178
Illinois	—	1	11	5	14	—	32	124	280	475	—	2	9	11	37
Indiana	—	0	0	—	—	—	13	62	94	175	—	3	10	25	18
Michigan	—	1	5	7	11	4	14	49	162	236	—	2	7	35	53
Ohio	2	0	12	9	5	24	24	47	312	362	7	2	11	43	32
Wisconsin	—	0	0	—	—	—	12	57	101	210	—	2	16	21	38
W.N. Central	2	3	40	25	80	28	49	121	542	700	5	14	49	100	161
Iowa	—	0	3	—	6	3	9	34	125	98	—	2	16	22	24
Kansas	—	1	4	11	23	2	7	19	84	100	—	1	5	18	14
Minnesota	—	0	34	—	13	—	10	30	—	216	—	4	20	—	36
Missouri	—	0	6	—	14	19	15	43	237	187	4	4	28	42	65
Nebraska [§]	2	1	3	10	21	4	4	13	54	52	1	1	6	15	15
North Dakota	—	0	6	4	3	—	0	13	—	6	—	0	10	—	—
South Dakota	—	0	0	—	—	—	3	17	42	41	—	0	4	3	7
S. Atlantic	36	19	37	357	457	202	261	624	2,624	2,630	20	16	31	272	151
Delaware	—	0	0	—	—	—	3	11	32	28	—	0	2	3	1
District of Columbia	—	0	0	—	—	—	1	7	10	32	—	0	2	1	3
Florida	—	0	29	40	121	87	108	226	1,111	1,246	11	6	15	131	53
Georgia	—	0	0	—	—	16	43	142	446	370	—	2	7	26	20
Maryland [§]	9	6	14	101	137	13	19	54	207	240	1	2	8	29	18
North Carolina	—	0	0	—	—	63	26	241	376	295	5	2	10	35	11
South Carolina [§]	—	0	0	—	—	15	25	99	197	175	—	0	4	9	5
Virginia [§]	27	12	26	216	171	8	21	68	226	186	3	3	9	37	37
West Virginia	—	0	7	—	28	—	1	14	19	58	—	0	4	1	3
E.S. Central	—	3	7	45	72	13	57	176	553	568	1	5	22	56	48
Alabama [§]	—	1	7	29	33	—	20	52	153	172	—	1	4	12	11
Kentucky	—	0	4	3	2	—	11	32	99	108	—	1	6	7	7
Mississippi	—	0	0	—	—	2	18	66	111	120	—	0	12	4	5
Tennessee [§]	—	1	4	13	37	11	18	53	190	168	1	2	7	33	25
W.S. Central	1	1	30	44	14	34	139	506	903	1,122	—	7	143	62	51
Arkansas [§]	1	0	10	33	10	19	12	43	137	80	—	1	4	7	12
Louisiana	—	0	0	—	—	2	19	49	141	262	—	0	2	3	5
Oklahoma	—	0	30	11	4	10	12	95	116	103	—	1	48	9	1
Texas [§]	—	0	0	—	—	3	95	381	509	677	—	5	95	43	33
Mountain	—	1	7	8	17	19	51	113	635	791	4	11	33	114	128
Arizona	—	0	2	—	—	—	16	43	214	242	—	1	14	28	23
Colorado	—	0	0	—	—	14	10	24	156	184	—	3	21	14	43
Idaho [§]	—	0	2	—	1	1	3	9	50	43	3	2	7	21	12
Montana [§]	—	0	3	5	—	3	1	6	27	32	1	0	3	7	15
Nevada [§]	—	0	2	—	—	1	5	21	51	63	—	0	6	14	7
New Mexico [§]	—	0	2	3	4	—	5	19	53	86	—	1	6	11	12
Utah	—	0	3	—	—	—	5	17	65	124	—	2	8	17	13
Wyoming [§]	—	0	4	—	12	—	1	8	19	17	—	0	3	2	3
Pacific	—	1	14	13	51	86	119	288	1,362	1,647	7	12	46	143	128
Alaska	—	0	2	9	11	—	1	4	23	29	—	0	1	—	1
California	—	0	12	—	36	54	82	232	1,020	1,116	4	7	36	104	60
Hawaii	—	0	0	—	—	8	6	13	98	101	—	0	3	2	14
Oregon	—	0	2	4	4	4	8	20	106	228	1	2	11	19	10
Washington	—	0	14	—	—	20	16	42	115	173	2	3	20	18	43
Territories															
American Samoa	N	0	0	N	N	—	0	1	—	1	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	3	6	1	—	0	0	—	—
Puerto Rico	2	0	2	10	20	—	6	21	22	191	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

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[†] Includes *E. coli* O157:H7; Shiga toxin-positive, serogroup non-O157; and Shiga toxin-positive, not serogrouped.

[§] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	Shigellosis						Spotted Fever Rickettsiosis (including RMSF) [†]								
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Confirmed				Probable					
		Med	Max			Current week	Previous 52 weeks	Cum 2011	Cum 2010	Current week	Previous 52 weeks	Cum 2011	Cum 2010		
United States	136	273	739	2,863	4,663	—	2	10	19	22	4	30	237	123	166
New England	—	4	17	57	151	—	0	0	—	—	—	0	1	1	1
Connecticut	—	0	9	9	69	—	0	0	—	—	—	0	0	—	—
Maine [§]	—	0	3	5	3	—	0	0	—	—	—	0	1	—	1
Massachusetts	—	3	16	42	67	—	0	0	—	—	—	0	0	—	—
New Hampshire	—	0	2	—	4	—	0	0	—	—	—	0	1	—	—
Rhode Island [§]	—	0	4	—	7	—	0	0	—	—	—	0	1	1	—
Vermont [§]	—	0	1	1	1	—	0	0	—	—	—	0	0	—	—
Mid. Atlantic	5	19	73	175	636	—	0	1	2	1	—	1	7	4	12
New Jersey	—	5	16	24	117	—	0	0	—	1	—	0	5	—	9
New York (Upstate)	3	3	15	40	59	—	0	1	—	—	—	0	3	1	2
New York City	1	5	14	77	117	—	0	0	—	—	—	0	2	2	1
Pennsylvania	1	6	55	34	343	—	0	1	2	—	—	0	3	1	—
E.N. Central	8	19	37	190	786	—	0	1	—	—	—	1	10	6	15
Illinois	—	7	20	55	552	—	0	1	—	—	—	0	5	3	6
Indiana [§]	—	1	5	24	21	—	0	1	—	—	—	0	5	—	6
Michigan	1	4	10	44	83	—	0	0	—	—	—	0	1	1	—
Ohio	7	5	18	67	91	—	0	0	—	—	—	0	2	2	2
Wisconsin	—	0	4	—	39	—	0	0	—	—	—	0	1	—	1
W.N. Central	10	18	81	131	1,024	—	0	2	2	1	1	4	17	23	34
Iowa	—	1	4	7	19	—	0	0	—	—	—	0	1	1	2
Kansas [§]	—	4	12	23	95	—	0	0	—	—	—	0	0	—	—
Minnesota	—	1	4	—	16	—	0	0	—	—	—	0	2	—	—
Missouri	10	10	65	97	880	—	0	2	2	1	1	4	17	22	31
Nebraska [§]	—	0	10	3	10	—	0	1	—	—	—	0	1	—	1
North Dakota	—	0	0	—	—	—	0	0	—	—	—	0	1	—	—
South Dakota	—	0	2	1	4	—	0	0	—	—	—	0	0	—	—
S. Atlantic	67	61	122	1,022	632	—	1	7	9	12	1	6	59	32	52
Delaware [§]	—	0	2	—	30	—	0	0	—	1	—	0	3	3	5
District of Columbia	—	0	3	6	15	—	0	1	1	—	—	0	0	—	—
Florida [§]	56	31	63	724	220	—	0	1	1	1	—	0	2	1	2
Georgia	3	15	26	140	226	—	0	6	3	8	—	0	0	—	—
Maryland [§]	—	2	8	29	39	—	0	1	1	—	—	0	5	3	6
North Carolina	6	3	36	76	43	—	0	3	1	2	—	2	47	12	29
South Carolina [§]	—	1	5	15	26	—	0	1	2	—	—	0	2	4	2
Virginia [§]	2	2	8	30	32	—	0	2	—	—	1	2	12	9	8
West Virginia	—	0	66	2	1	—	0	0	—	—	—	0	0	—	—
E.S. Central	1	14	40	160	229	—	0	3	—	5	1	5	30	35	41
Alabama [§]	1	5	15	59	32	—	0	1	—	—	—	1	9	9	6
Kentucky	—	2	28	25	92	—	0	2	—	4	—	0	0	—	—
Mississippi	—	1	5	36	12	—	0	0	—	—	—	0	4	—	2
Tennessee [§]	—	4	14	40	93	—	0	2	—	1	1	4	20	26	33
W.S. Central	28	55	501	554	696	—	0	7	—	1	1	2	227	4	10
Arkansas [§]	2	2	7	22	14	—	0	2	—	—	—	0	28	1	4
Louisiana	—	5	13	49	74	—	0	0	—	—	—	0	1	—	—
Oklahoma	—	3	160	34	110	—	0	4	—	—	1	0	194	2	2
Texas [§]	26	44	337	449	498	—	0	1	—	1	—	0	5	1	4
Mountain	6	17	32	252	196	—	0	5	6	—	—	0	7	18	1
Arizona	1	7	19	61	106	—	0	4	6	—	—	0	7	18	—
Colorado [§]	2	2	8	33	21	—	0	1	—	—	—	0	1	—	—
Idaho [§]	—	0	3	7	6	—	0	0	—	—	—	0	1	—	—
Montana [§]	3	0	15	86	4	—	0	1	—	—	—	0	1	—	—
Nevada [§]	—	0	6	6	11	—	0	0	—	—	—	0	0	—	—
New Mexico [§]	—	3	10	43	38	—	0	0	—	—	—	0	0	—	1
Utah	—	1	4	16	10	—	0	0	—	—	—	0	1	—	—
Wyoming [§]	—	0	0	—	—	—	0	0	—	—	—	0	1	—	—
Pacific	11	23	63	322	313	—	0	2	—	2	—	0	1	—	—
Alaska	—	0	1	1	—	N	0	0	N	N	N	0	0	N	N
California	3	19	59	246	245	—	0	2	—	2	—	0	0	—	—
Hawaii	1	1	4	25	22	N	0	0	N	N	N	0	0	N	N
Oregon	—	1	4	24	22	—	0	0	—	—	—	0	1	—	—
Washington	7	1	22	26	24	—	0	1	—	—	—	0	0	—	—
Territories															
American Samoa	—	1	1	1	1	N	0	0	N	N	N	0	0	N	N
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	1	1	—	N	0	0	N	N	N	0	0	N	N
Puerto Rico	—	0	1	—	1	N	0	0	N	N	N	0	0	N	N
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

[†] Illnesses with similar clinical presentation that result from Spotted fever group rickettsia infections are reported as Spotted fever rickettsioses. Rocky Mountain spotted fever (RMSF) caused by *Rickettsia rickettsii*, is the most common and well-known spotted fever.

[§] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	<i>Streptococcus pneumoniae</i> , [†] invasive disease										Syphilis, primary and secondary				
	All ages				Age <5										
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	211	289	972	6,521	8,101	24	32	117	584	1,116	68	253	354	3,802	4,653
New England	4	11	79	162	395	—	1	9	12	61	1	9	19	133	163
Connecticut	—	0	49	—	184	—	0	7	—	21	—	1	8	18	33
Maine [§]	2	2	13	54	60	—	0	1	2	5	—	0	3	8	14
Massachusetts	—	0	5	14	44	—	0	3	6	31	—	5	14	81	100
New Hampshire	—	2	8	50	62	—	0	1	1	3	1	0	3	12	6
Rhode Island [§]	—	0	36	8	8	—	0	3	—	—	—	0	4	10	8
Vermont [§]	2	1	6	36	37	—	0	1	3	1	—	0	2	4	2
Mid. Atlantic	14	31	69	670	731	2	4	21	75	121	4	31	46	434	625
New Jersey	—	2	8	35	60	—	1	5	19	27	1	4	10	61	89
New York (Upstate)	2	2	10	38	80	2	1	9	21	59	2	3	20	67	33
New York City	6	13	36	307	344	—	0	12	9	8	—	15	29	189	361
Pennsylvania	6	12	24	290	247	—	1	5	26	27	1	7	16	117	142
E.N. Central	34	64	111	1,459	1,580	2	6	12	123	184	—	30	56	304	693
Illinois	—	2	6	39	52	—	2	6	39	46	—	14	23	52	350
Indiana	—	9	29	263	339	—	0	4	13	31	—	3	14	48	50
Michigan	4	13	29	313	343	—	1	4	20	44	—	4	10	69	109
Ohio	26	25	45	631	608	2	2	7	43	46	—	9	21	121	166
Wisconsin	4	9	24	213	238	—	0	3	8	17	—	1	3	14	18
W.N. Central	8	13	40	186	551	—	2	7	28	93	2	7	18	108	103
Iowa	—	0	0	—	—	—	0	0	—	—	—	0	3	4	6
Kansas	4	2	6	45	73	—	0	2	3	10	—	0	3	5	8
Minnesota	—	5	24	—	318	—	1	5	—	47	—	3	10	44	23
Missouri	—	3	10	84	63	—	1	4	22	22	2	2	9	53	62
Nebraska [§]	4	2	9	57	62	—	0	1	3	8	—	0	2	2	4
North Dakota	—	0	13	—	23	—	0	1	—	—	—	0	0	—	—
South Dakota	—	0	2	—	12	—	0	2	—	6	—	0	1	—	—
S. Atlantic	38	70	173	1,533	2,164	7	7	25	133	289	22	63	166	1,042	1,060
Delaware	—	1	6	27	17	—	0	1	—	—	—	0	4	4	3
District of Columbia	1	1	4	26	44	—	0	2	3	6	2	3	8	69	50
Florida	20	25	68	734	803	3	3	13	65	102	2	23	44	384	384
Georgia	4	15	54	200	703	1	2	7	17	80	—	11	118	131	204
Maryland [§]	8	9	32	275	244	2	1	4	14	31	5	7	17	160	84
North Carolina	—	0	0	—	—	—	0	0	—	—	7	7	19	137	178
South Carolina [§]	5	8	25	252	269	1	1	3	15	30	4	3	10	74	46
Virginia [§]	—	1	4	19	30	—	1	4	19	30	2	4	16	83	108
West Virginia	—	0	14	—	54	—	0	6	—	10	—	0	2	—	3
E.S. Central	16	23	45	539	652	2	2	6	35	65	7	14	39	203	310
Alabama [§]	—	0	0	—	—	—	0	0	—	—	1	3	11	35	101
Kentucky	—	3	11	74	83	—	0	3	10	5	4	2	16	39	31
Mississippi	—	1	8	10	33	—	0	2	—	6	1	3	16	44	69
Tennessee [§]	16	19	36	455	536	2	1	4	25	54	1	5	11	85	109
W.S. Central	73	31	370	892	907	8	4	38	99	145	19	37	71	567	700
Arkansas [§]	3	3	27	120	86	—	0	3	10	11	2	3	10	65	96
Louisiana	—	2	11	97	54	—	0	2	8	17	2	8	36	100	135
Oklahoma	1	1	8	17	29	1	1	8	17	29	1	1	6	18	32
Texas [§]	69	25	333	658	738	7	3	27	64	88	14	23	33	384	437
Mountain	23	34	75	916	989	3	3	8	68	139	3	11	24	130	185
Arizona	5	12	43	419	471	2	1	5	28	60	—	4	9	9	74
Colorado	17	10	23	232	260	1	1	3	14	37	1	2	8	41	47
Idaho [§]	—	0	2	4	8	—	0	2	3	4	—	0	2	3	2
Montana [§]	—	0	2	7	8	—	0	1	1	—	—	0	2	1	—
Nevada [§]	—	2	8	56	37	—	0	1	3	4	2	3	9	50	30
New Mexico [§]	—	3	13	121	85	—	0	2	9	12	—	1	4	21	8
Utah	—	4	8	63	110	—	0	3	10	20	—	0	5	5	24
Wyoming [§]	1	0	15	14	10	—	0	1	—	2	—	0	0	—	—
Pacific	1	6	24	164	132	—	0	5	11	19	10	51	65	881	814
Alaska	—	2	11	60	61	—	0	2	5	16	—	0	1	—	2
California	1	4	23	103	71	—	0	5	6	3	6	42	57	709	697
Hawaii	—	0	3	1	—	—	0	0	—	—	—	0	5	5	14
Oregon	—	0	0	—	—	—	0	0	—	—	1	1	7	37	23
Washington	—	0	0	—	—	—	0	0	—	—	3	6	14	130	78
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	0	0	—	—	—	0	0	—	—	—	4	15	75	76
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/ndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

† Includes drug resistant and susceptible cases of invasive *Streptococcus pneumoniae* disease among children <5 years and among all ages. Case definition: Isolation of *S. pneumoniae* from a normally sterile body site (e.g., blood or cerebrospinal fluid).

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending May 14, 2011, and May 15, 2010 (19th week)*

Reporting area	West Nile virus disease [†]														
	Varicella (chickenpox)					Neuroinvasive					Nonneuroinvasive [‡]				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	175	235	583	4,233	6,946	—	1	71	—	1	—	0	53	—	4
New England	1	18	46	245	435	—	0	3	—	—	—	0	2	—	—
Connecticut	—	3	15	—	120	—	0	2	—	—	—	0	2	—	—
Maine [§]	—	4	16	—	88	—	0	0	—	—	—	0	0	—	—
Massachusetts	—	5	17	103	115	—	0	2	—	—	—	0	1	—	—
New Hampshire	—	2	9	9	56	—	0	1	—	—	—	0	0	—	—
Rhode Island [¶]	—	0	4	6	11	—	0	0	—	—	—	0	0	—	—
Vermont [¶]	1	2	13	39	35	—	0	0	—	—	—	0	0	—	—
Mid. Atlantic	17	27	62	476	714	—	0	19	—	—	—	0	13	—	—
New Jersey	—	8	23	122	266	—	0	3	—	—	—	0	6	—	—
New York (Upstate)	N	0	0	N	N	—	0	9	—	—	—	0	7	—	—
New York City	—	0	0	—	1	—	0	7	—	—	—	0	4	—	—
Pennsylvania	17	18	41	354	447	—	0	3	—	—	—	0	3	—	—
E.N. Central	43	70	153	1,316	2,495	—	0	15	—	—	—	0	7	—	—
Illinois	5	17	41	328	639	—	0	10	—	—	—	0	4	—	—
Indiana [¶]	—	5	19	99	217	—	0	2	—	—	—	0	2	—	—
Michigan	10	23	43	413	764	—	0	6	—	—	—	0	1	—	—
Ohio	28	21	58	475	627	—	0	1	—	—	—	0	1	—	—
Wisconsin	—	5	22	1	248	—	0	0	—	—	—	0	1	—	—
W.N. Central	7	11	35	169	383	—	0	7	—	—	—	0	11	—	1
Iowa	N	0	0	N	N	—	0	1	—	—	—	0	2	—	—
Kansas [¶]	2	2	18	51	178	—	0	1	—	—	—	0	3	—	1
Minnesota	—	0	0	—	—	—	0	1	—	—	—	0	3	—	—
Missouri	—	7	24	90	172	—	0	1	—	—	—	0	0	—	—
Nebraska [¶]	N	0	0	N	N	—	0	3	—	—	—	0	7	—	—
North Dakota	5	0	10	16	23	—	0	2	—	—	—	0	2	—	—
South Dakota	—	1	7	12	10	—	0	2	—	—	—	0	3	—	—
S. Atlantic	28	32	99	593	935	—	0	6	—	—	—	0	4	—	3
Delaware [¶]	—	0	4	3	12	—	0	0	—	—	—	0	0	—	—
District of Columbia	—	0	3	8	8	—	0	1	—	—	—	0	1	—	—
Florida [¶]	23	15	57	420	476	—	0	3	—	—	—	0	1	—	—
Georgia	N	0	0	N	N	—	0	1	—	—	—	0	3	—	3
Maryland [¶]	N	0	0	N	N	—	0	3	—	—	—	0	2	—	—
North Carolina	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
South Carolina [¶]	—	0	6	—	68	—	0	1	—	—	—	0	0	—	—
Virginia [¶]	5	9	29	162	183	—	0	1	—	—	—	0	1	—	—
West Virginia	—	4	23	—	188	—	0	0	—	—	—	0	0	—	—
E.S. Central	8	6	16	126	132	—	0	1	—	1	—	0	3	—	—
Alabama [¶]	8	5	16	118	131	—	0	1	—	—	—	0	1	—	—
Kentucky	N	0	0	N	N	—	0	1	—	—	—	0	1	—	—
Mississippi	—	0	3	8	1	—	0	1	—	1	—	0	2	—	—
Tennessee [¶]	N	0	0	N	N	—	0	1	—	—	—	0	2	—	—
W.S. Central	65	40	258	894	1,261	—	0	16	—	—	—	0	3	—	—
Arkansas [¶]	—	3	17	82	102	—	0	3	—	—	—	0	1	—	—
Louisiana	—	1	4	13	34	—	0	3	—	—	—	0	1	—	—
Oklahoma	N	0	0	N	N	—	0	1	—	—	—	0	0	—	—
Texas [¶]	65	37	247	799	1,125	—	0	15	—	—	—	0	2	—	—
Mountain	6	15	50	334	548	—	0	18	—	—	—	0	15	—	—
Arizona	—	0	0	—	—	—	0	13	—	—	—	0	9	—	—
Colorado [¶]	4	6	31	118	194	—	0	5	—	—	—	0	11	—	—
Idaho [¶]	N	0	0	N	N	—	0	0	—	—	—	0	1	—	—
Montana [¶]	—	2	28	84	94	—	0	0	—	—	—	0	0	—	—
Nevada [¶]	N	0	0	N	N	—	0	0	—	—	—	0	1	—	—
New Mexico [¶]	2	1	8	18	52	—	0	6	—	—	—	0	2	—	—
Utah	—	4	26	107	198	—	0	1	—	—	—	0	1	—	—
Wyoming [¶]	—	0	3	7	10	—	0	1	—	—	—	0	1	—	—
Pacific	—	3	22	80	43	—	0	8	—	—	—	0	6	—	—
Alaska	—	1	5	24	15	—	0	0	—	—	—	0	0	—	—
California	—	0	19	36	13	—	0	8	—	—	—	0	6	—	—
Hawaii	—	1	4	20	15	—	0	0	—	—	—	0	0	—	—
Oregon	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
Washington	N	0	0	N	N	—	0	1	—	—	—	0	1	—	—
Territories															
American Samoa	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	4	16	8	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	6	30	50	182	—	0	0	—	—	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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† Updated weekly from reports to the Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ArboNET Surveillance). Data for California serogroup, eastern equine, Powassan, St. Louis, and western equine diseases are available in Table I.

‡ Not reportable in all states. Data from states where the condition is not reportable are excluded from this table, except starting in 2007 for the domestic arboviral diseases and influenza-associated pediatric mortality, and in 2003 for SARS-CoV. Reporting exceptions are available at http://www.cdc.gov/osels/ph_surveillance/nndss/phs/infdss.htm.

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE III. Deaths in 122 U.S. cities,* week ending May 14, 2011 (19th week)

Reporting area	All causes, by age (years)						P&I [†] Total	Reporting area (Continued)	All causes, by age (years)						P&I [†] Total
	All Ages	≥65	45-64	25-44	1-24	<1			All Ages	≥65	45-64	25-44	1-24	<1	
New England	516	363	104	29	8	12	48	S. Atlantic	1,298	813	350	89	23	22	109
Boston, MA	133	86	34	7	2	4	12	Atlanta, GA	159	87	45	18	5	4	13
Bridgeport, CT	33	26	4	2	—	1	1	Baltimore, MD	174	104	46	13	6	5	22
Cambridge, MA	9	8	—	1	—	—	2	Charlotte, NC	134	77	39	13	2	3	13
Fall River, MA	18	13	4	1	—	—	1	Jacksonville, FL	166	113	46	4	2	1	16
Hartford, CT	50	33	13	2	1	1	4	Miami, FL	100	75	20	5	—	—	7
Lowell, MA	19	14	1	4	—	—	2	Norfolk, VA	54	32	14	4	—	4	2
Lynn, MA	8	5	2	1	—	—	—	Richmond, VA	57	37	16	3	1	—	4
New Bedford, MA	32	24	7	1	—	—	3	Savannah, GA	62	36	20	5	—	—	3
New Haven, CT	49	30	14	2	1	2	6	St. Petersburg, FL	57	40	12	3	2	—	4
Providence, RI	60	45	10	4	1	—	7	Tampa, FL	188	126	48	10	2	2	16
Somerville, MA	2	2	—	—	—	—	—	Washington, D.C.	125	71	38	10	3	3	8
Springfield, MA	26	20	1	1	1	3	6	Wilmington, DE	22	15	6	1	—	—	1
Waterbury, CT	25	17	5	3	—	—	1	E.S. Central	932	579	257	64	19	13	71
Worcester, MA	52	40	9	—	2	1	3	Birmingham, AL	165	104	45	11	3	2	16
Mid. Atlantic	1,773	1,224	390	85	40	33	92	Chattanooga, TN	96	70	15	6	2	3	5
Albany, NY	54	42	10	—	1	1	6	Knoxville, TN	122	82	27	7	3	3	9
Allentown, PA	20	18	2	—	—	—	3	Lexington, KY	78	43	29	6	—	—	5
Buffalo, NY	88	59	23	2	1	3	3	Memphis, TN	189	113	58	11	5	2	16
Camden, NJ	31	17	10	3	—	1	3	Mobile, AL	112	62	37	11	2	—	7
Elizabeth, NJ	17	12	5	—	—	—	1	Montgomery, AL	38	21	15	2	—	—	3
Erie, PA	27	20	7	—	—	—	1	Nashville, TN	132	84	31	10	4	3	10
Jersey City, NJ	18	11	5	2	—	—	—	W.S. Central	1,382	856	347	101	32	46	90
New York City, NY	912	621	207	42	24	17	40	Austin, TX	99	68	18	6	3	4	4
Newark, NJ	35	24	8	1	2	—	3	Baton Rouge, LA	65	44	13	8	—	—	2
Paterson, NJ	34	20	10	2	—	2	3	Corpus Christi, TX	73	47	15	9	1	1	5
Philadelphia, PA	238	149	57	21	4	7	12	Dallas, TX	188	111	41	13	10	13	6
Pittsburgh, PA [§]	36	28	7	1	—	—	1	El Paso, TX	118	79	29	8	1	1	15
Reading, PA	33	27	5	—	1	—	1	Fort Worth, TX	U	U	U	U	U	U	U
Rochester, NY	70	58	6	3	3	—	4	Houston, TX	302	166	94	19	6	17	19
Schenectady, NY	19	13	6	—	—	—	1	Little Rock, AR	81	49	18	8	1	5	—
Scranton, PA	19	17	2	—	—	—	1	New Orleans, LA	U	U	U	U	U	U	U
Syracuse, NY	69	54	10	3	—	2	4	San Antonio, TX	261	170	64	19	4	4	15
Trenton, NJ	16	9	7	—	—	—	—	Shreveport, LA	57	32	17	4	3	1	8
Utica, NY	20	10	1	5	4	—	1	Tulsa, OK	138	90	38	7	3	—	16
Yonkers, NY	17	15	2	—	—	—	4	Mountain	1,037	730	211	58	22	14	50
E.N. Central	1,931	1,298	449	103	45	36	138	Albuquerque, NM	99	76	17	2	2	2	9
Akron, OH	53	33	13	4	1	2	7	Boise, ID	63	49	10	2	—	2	2
Canton, OH	35	26	7	—	2	—	5	Colorado Springs, CO	91	72	16	2	1	—	1
Chicago, IL	256	173	62	17	4	—	21	Denver, CO	107	65	27	7	5	3	4
Cincinnati, OH	76	40	22	4	7	3	5	Las Vegas, NV	293	192	71	21	5	4	11
Cleveland, OH	226	163	46	10	2	5	9	Ogden, UT	38	25	8	3	—	2	4
Columbus, OH	177	122	36	11	3	5	17	Phoenix, AZ	U	U	U	U	U	U	U
Dayton, OH	125	92	28	2	3	—	8	Pueblo, CO	37	26	5	3	3	—	3
Detroit, MI	162	78	59	13	9	3	8	Salt Lake City, UT	126	89	24	9	3	1	7
Evansville, IN	52	37	11	3	1	—	1	Tucson, AZ	183	136	33	9	3	—	9
Fort Wayne, IN	72	48	20	3	1	—	7	Pacific	1,839	1,305	389	98	26	21	187
Gary, IN	16	10	6	—	—	—	—	Berkeley, CA	12	7	4	1	—	—	1
Grand Rapids, MI	56	47	7	1	—	1	5	Fresno, CA	129	84	33	8	—	4	13
Indianapolis, IN	182	118	42	10	2	10	8	Glendale, CA	33	28	3	2	—	—	6
Lansing, MI	48	32	10	1	5	—	8	Honolulu, HI	68	55	8	5	—	—	6
Milwaukee, WI	88	57	20	8	1	2	3	Long Beach, CA	76	49	23	2	2	—	13
Peoria, IL	50	38	7	4	—	1	8	Los Angeles, CA	251	164	52	20	12	3	20
Rockford, IL	61	45	11	3	—	2	5	Pasadena, CA	26	19	6	1	—	—	2
South Bend, IN	53	34	13	3	2	1	4	Portland, OR	135	93	34	5	1	2	10
Toledo, OH	91	67	15	6	2	1	8	Sacramento, CA	225	156	56	9	1	3	35
Youngstown, OH	52	38	14	—	—	—	1	San Diego, CA	189	136	40	9	3	1	19
W.N. Central	592	413	132	22	8	17	40	San Francisco, CA	124	88	28	5	1	2	12
Des Moines, IA	80	61	15	—	1	3	8	San Jose, CA	198	152	30	11	4	1	21
Duluth, MN	36	24	9	3	—	—	4	Santa Cruz, CA	32	25	5	2	—	—	6
Kansas City, KS	27	16	8	1	—	2	—	Seattle, WA	108	73	23	8	1	3	2
Kansas City, MO	102	69	19	7	1	6	3	Spokane, WA	75	65	5	3	—	2	10
Lincoln, NE	41	33	7	—	1	—	3	Tacoma, WA	158	111	39	7	1	—	11
Minneapolis, MN	55	33	16	1	3	2	4	Total[¶]	11,300	7,581	2,629	649	223	214	825
Omaha, NE	124	85	30	7	1	1	10								
St. Louis, MO	2	1	1	—	—	—	—								
St. Paul, MN	60	44	11	3	—	2	6								
Wichita, KS	65	47	16	—	1	1	2								

U: Unavailable. —: No reported cases.

* Mortality data in this table are voluntarily reported from 122 cities in the United States, most of which have populations of >100,000. A death is reported by the place of its occurrence and by the week that the death certificate was filed. Fetal deaths are not included.

[†] Pneumonia and influenza.

[§] Because of changes in reporting methods in this Pennsylvania city, these numbers are partial counts for the current week. Complete counts will be available in 4 to 6 weeks.

[¶] Total includes unknown ages.

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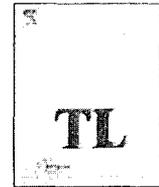
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Mini review

3,4-Methylenedioxypropylvalerone (MDPV): Chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online

M. Coppola^{a,*}, R. Mondola^b

^a Department of Addiction, ASL CN2, Viale Coppino 46, 12051, Alba (CN), Italy

^b Department of Mental Health, ASL CN1, Via Torino 70/B, 12037 Saluzzo (CN), Italy

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ABSTRACT

The illicit marketplace of substances of abuse continually offers for sale legal alternatives to controlled drugs to a large public. In recent years, a new group of designer drugs, the synthetic cathinones, has emerged as a new trend, particularly among young people. The 3,4-methylenedioxypropylvalerone (MDPV), one of this synthetic compounds, caused an international alert for its cardiovascular and neurological toxicity. This substance, sold as bath salts, has caused many serious intoxications and some deaths in several countries. The aim of this paper is summarise the clinical, pharmacological and toxicological information about this new designer drug.

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Contents

1. Introduction	12
2. Synthetic cathinones, <i>Catha edulis</i> (khat) and natural cathinones	13
2.1. Synthetic cathinones	13
2.2. <i>Catha edulis</i> (khat) and natural cathinones	13
3. 3,4-Methylenedioxypropylvalerone (MDPV)	13
3.1. Chemistry	13
3.2. Pharmacology	13
3.3. Toxicology	13
4. Internet information	14
5. Legal status	14
6. Discussion	14
7. Conclusion	14
Conflict of interest statement	14
References	14

1. Introduction

The illicit marketplace of substances of abuse continually offers for sale legal alternatives to controlled drugs to a large public. These psychoactive substances are both synthetic derivatives and vegetable compounds that can produce important public health consequences and policy implications (Collins, 2011). Furthermore, the internet has emerged as a new marketplace for the spread

of these products and its monitoring is an important instrument to identify new trends of drugs of abuse (Schifano et al., 2010). Recent information have shown that the online market is able to respond rapidly to changes in the legal status of the psychoactive drugs offering for sale new legal alternatives (Walsh, 2011). After the development of synthetic derivatives based on fentanyl in the 1980s, ring-substituted phenethylamines in the late 1980s, tryptamines in 1990s and piperazines in the 2000s, in recent years, a new group of designer drugs, the synthetic cathinones, has emerged as a new trend, particularly among young people (Brandt et al., 2010). Synthetic cathinones are a group of synthetic derivatives of the vegetable cathinone, a phenylalkylamine

* Corresponding author. Tel.: +39 0173316210; fax: +39 0173420344.
E-mail address: coppolamail@alice.it (M. Coppola).

alkaloid naturally present in the *Catha edulis* (khat) (Hassan et al., 2007). The first synthetic cathinone which has had a large diffusion in the population was the maphedrone, a psychoactive substance that has produced many serious intoxication and some deaths in various countries (Hadlock et al., 2011). When the legal status of this compound changed, another synthetic cathinone, the 3,4-methylenedioxypropylvalerone (MDPV), received a large diffusion among young people causing a new international alert (ISS, 2011). The aim of this paper is summarise the clinical, pharmacological and toxicological information about this new designer drug.

2. Synthetic cathinones, *Catha edulis* (khat) and natural cathinones

2.1. Synthetic cathinones

Synthetic cathinones are the beta-keto analogues of the natural cathinone, one of the psychoactive compounds present in khat, in particular, most of the synthetic cathinones appeared in the recreational drug market since the mid-2000s are a ring-substituted cathinone closely related to the phenethylamine family, differing only by a keto functional group at the beta carbon (namsdl, 2011). Like the related phenethylamines, synthetic cathinones can exist in two stereoisomeric forms that may have different potency and it is likely that some ring-substituted derivatives could be racemic mixtures (Gibbons and Zloh, 2010). Synthetic cathinones produce amphetamine-like effects because they inhibit the reuptake of and stimulate the release of norepinephrine, serotonin and dopamine (Cozzi et al., 1999; Kehr et al., 2011). These molecules are used as substitute for other stimulants such as amphetamines, cocaine or ecstasy because, although they are generally less lipophilic and less able to cross the blood–brain barrier (pyrrolidine derivatives such as pyrovalerone or MDPV are more lipophilic and more able to cross the blood–brain barrier than other synthetic cathinones), they can produce the same effects on the Central Nervous System (Dargan et al., 2011). The studies on the metabolism of cathinone derivatives in rats and humans have shown that they are N-demethylated, the keto group is reduced to hydroxyl and ring alkyl groups are oxidised (Meyer and Maurer, 2010). The users can snort or ingest these white or brown amorphous or crystalline powders, but since they are soluble in water, these substances can also be injected (Winstock et al., 2011; Schifano et al., 2011). In recent years, the assumption of synthetic cathinones has been associated with several cases of toxicity and deaths (James et al., 2010). Clinical features include neurological, cardiovascular and psychopathological symptoms such as: psychomotor agitation, delusions, hallucinations, psychosis, hypertension, palpitation, chest pain, seizures, headaches (Wood et al., 2010). Synthetic cathinones include several substances that have been used as research chemical, but only three compounds are used as medicinal products: amfepramone (obesity), pyrovalerone (obesity and chronic fatigue) and bupropion (depression and tobacco dependence), the others are used only for recreational scope (pharmacocode-amfepramone, 2011; pharmacocode-bupropion, 2011; Gordons and Cole, 1971).

2.2. *Catha edulis* (khat) and natural cathinones

Catha edulis, simply called khat, is an evergreen slow-growing shrub or tree native to Ethiopia and cultivated in East Africa and South West Arabian Peninsula that in recent years has been widespread in Europe too (emcdda, 2011). The people living in khat geographical areas use the fresh vegetable material (leaves, stems, flower buds) of this plant for its stimulant effects (Kalix, 1992). The fresh khat leaves contain 62 alkaloids and for two of these, cathine

and cathinone, have been demonstrated amphetamine-like effects, particularly, these phenylalkylamine alkaloids cause the release of catecholamines from pre-synaptic storage sites in the central and peripheral nervous system (Kalix, 1986). In addition, these alkaloids may also have monoamine oxidase inhibition effects (Nencini et al., 1984). Cathine and cathinone determine in humans increased in blood pressure and in heart rate, euphoria and psychomotor hyperactivity (Brenneisen et al., 1990). Several studies have shown the harmful effects of this plant such as: increased incidence of acute coronary vasospasm and myocardial infarction, oesophagitis, gastritis, oral keratotic lesions and liver toxicity (Al-Habori, 2005). Furthermore, insomnia, depression, anorexia, psychosis and impaired working memory have been reported after occasional or chronic use of khat (Balint et al., 2009; Colzato et al., 2011).

3. 3,4-Methylenedioxypropylvalerone (MDPV)

3.1. Chemistry

The MDPV is a pyrrolidine derivative of the synthetic cathinone pyrovalerone differing for the presence of a 3,4-methylenedioxy group linked to the aromatic ring in substitution of a 4-methyl group (Yohannan and Bozenko, 2010) that was synthesized by Boehringer Ingelheim and patented in 1969 and first seized in Germany in the year 2007 (Westphal et al., 2009). This compound, IUPAC name 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-ylpentan-1-one, is a white (HCL salt form), brown or yellow-green (free base form) or gray (european form) amorphous or crystalline powder with a molecular weight of 275.34284 g/mol classified as a research chemical (pubchem, 2011). The MDPV includes in its chemical structure a nitrogen atom attached to three carbon atoms composing a tertiary amino group that is responsible of the high solubility of this compound in organic solvents, in particular the free base (caymanchem, 2011).

3.2. Pharmacology

Like pyrovalerone, MDPV is a monoamine uptake inhibitor more lipophilic and more potent than other cathinone derivatives (Meltzer et al., 2006). The high lipophilicity of this substance is caused by the pyrrolidine ring and the tertiary amino group creating a less polar molecule more able to cross the blood–brain barrier (emcdda, 2010). The metabolism of MDPV was evaluated in vitro using human liver microsomes and S9 cellular fractions for CYP450 phase I and uridine 5-diphosphoglucuronosyltransferase and sulfotransferase for the phase II metabolism. This study has demonstrated that the main metabolites of MDPV are catechol and methyl-catechol pyrovalerone which are in turn sulfated and glucuronated (Strano-rossi et al., 2011).

3.3. Toxicology

There are limited information about the short and long-term toxicological effects of this designer drug of abuse. The action of MDPV on monoamine reuptake may produce stimulant effects like cocaine, amphetamines or ecstasy, particularly, the stimulant effect has been compared to methylphenidate, at low doses, and cocaine or amphetamines, at high doses (scribd, 2011). In literature have been reported acute toxicity episodes and deaths related to MDPV assumption in several countries (acep, 2011). Acute toxicity mainly includes neurological, cardiovascular and psychopathological symptoms such as: tachycardia, chest pain, S-T segment changes, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, parkinsonism, delusions, hallucinations, paranoid psychosis, depression, panic attacks,

long term changes in cognition and emotional stability, rhabdomyolysis, abdominal pain, vomiting, kidney damage (Durham, 2011; CDC, 2011; Penders and Gestring, 2011). The treatment generally includes low or moderate doses of a benzodiazepine to control the signs of toxicity and antipsychotics or propofol when this medicament is ineffective (Spiller et al., 2011). Furthermore, it was reported the development of craving, tolerance, dependence and withdrawal syndrome after the frequent consumption of high doses of MDPV (CDC, 2011). The MDPV is not detected via standard drug tests but it is required the gas chromatography/mass spectrometry (GS/MS) (Ojanpera et al., 2011).

4. Internet information

The online discussion about MDPV seems begun around 2004, but the popularity of this substance increased in late 2008 (drugguide, 2011; drugs-forum, 2011). Users reported soft Central Nervous System stimulant effects of MDPV at low doses, but very strong stimulant effects at high doses, more potent than cocaine or amphetamines (drugs-forum, 2011; erowid, 2011). There were many reports of people that have used low doses of MDPV to increase the concentration, capacity to work or study, sexual performance (drugs-forum, 2011; erowid, 2011). Other desired psychoactive effects include: increased sociability, energy, limited euphoria, mild empathogenic effects (drugrecognitionexpert, 2011). Users also reported untoward effects such as: prolonged panic attack, tremor, agitation, insomnia, nausea, headache, tinnitus, dizziness, increased heart rate, altered vision, confusion, suicidal thoughts, anhedonia, depression, psychosis, risk of tolerance and dependence (drugs-forum, 2011; erowid, 2011; zoklet, 2011). Internet information also reported some discussion about the combination of MDPV with other drugs in order to reduce the harmful effects or enhance the desired effects. In particular, the most discussed combination are between MDPV and alcohol, propranolol or other beta blocker (to counteract tachycardia) GHB, 5-MeO-MIPT (as an aphrodisiac), GBL, zopiclone (to produce visual hallucinations), kratom, hallucinogenes, amphetamines (to enhance stimulant and entactogen effects), pregabalin, famotidine, omeprazole, domperidone (to counteract stomach pain), opiates (speedball like-effects), cannabis, benzodiazepines (to counteract anxiety) and other synthetic compounds (e.g. mephedrone, methylone) (drugs-forum, 2011). The modalities of administration include: oral ingestion, sublingual, intravenous, intramuscular, smoking, insufflation (snorting), inhalation and it has been reported the rectal administration (drugs-forum, 2011; erowid, 2011). Independently of the modalities of intake, the psychoactive effects may be the same, but non-oral assumption could produce shorter duration of action (drugs-forum, 2011). Some users suggest that 1 mg or 2 mg of MDPV are able to produce psychoactive effects (sublingual, rectal or inhalation assumption), but the typical doses range appear to be between 5 and 30 mg in a single ingestion. Redosing in a single session is very common because MDPV have a short duration of action (doses higher to 200 mg in a single session have been reported) (drugs-forum, 2011; bluelight, 2011; erowid, 2011).

5. Legal status

The MDPV is not approved as therapeutic drug and it is a controlled substance in Sweden (2010), Denmark (2009), Ireland (2010), United Kingdom (2010), Germany (2010), Australia (2010), Finland (2010), Israel and Italy. In addition this substance is controlled in some States of United States of America such as: Alabama, Florida, Idaho, Louisiana, Michigan, Mississippi, New Jersey, North Carolina, North Dakota and Utah (2011) (sostanze.info, 2011; drugs-forum, 2011).

6. Discussion

The MDPV is a catecholamines reuptake inhibitor derived by pyrovalerone with strong stimulant effects. This compound, classified as research chemical, can be considered a new designer drug of abuse. Little is known about the clinical, pharmacological and toxicological effects of MDPV, but some reports and the information on drugs forum suggest that its stimulant action could be more potent than cocaine or amphetamines. These psychoactive effects may justify the widespread of this compound as recreational drug, particularly among young people. Furthermore, the legal status of MDPV in several countries, the wide availability on the online market and the difficulty of identification in biological materials have favored the use of this synthetic cathinone as alternative to other illicit stimulants. Finally, the marketing of MDPV as bath salts or plants fertilizer provided false assurances on the safety of this substance as drug of abuse. The literature data and internet information have shown the high Cardiovascular and Central Nervous Systems acute toxicity of MDPV related to the powerful stimulation of the catecholaminergic system (Meltzer et al., 2006; Durham, 2011). Furthermore, the dopaminergic stimulation in the reward system could explain the development of tolerance, abuse, dependence and withdrawal syndrome reported by users (Ross and Peselow, 2009). Thus, considering the limited information about the clinical, pharmacological and toxicological effects of this substance in combination with the potential health risks, the alertness of scientific community is of great importance in order to monitoring and prevent the spread of MDPV.

7. Conclusion

In this paper we reviewed literature data and internet information about the clinical, pharmacological and toxicological effects of MDPV. Although this substance is marketed as bath salts or plants fertilizer, the drug users utilize the MDPV for its cocaine and amphetamine-like effects. Furthermore, in several countries MDPV is a legal alternative to illicit stimulants used by people that are afraid of the judicial consequences of the controlled substances assumption. Clinical reports and internet information clearly demonstrate the acute Cardiovascular and Central Nervous Systems toxicity of MDPV in combination with the high risk of death drug-related, abuse, tolerance and dependence. Scientific community must monitorate the diffusion of MDPV and it should use the information on drugs forum to identify new trends of substances of abuse early. In conclusion, the data currently available suggest that the recreational use of MDPV must be considered highly dangerous to public health.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

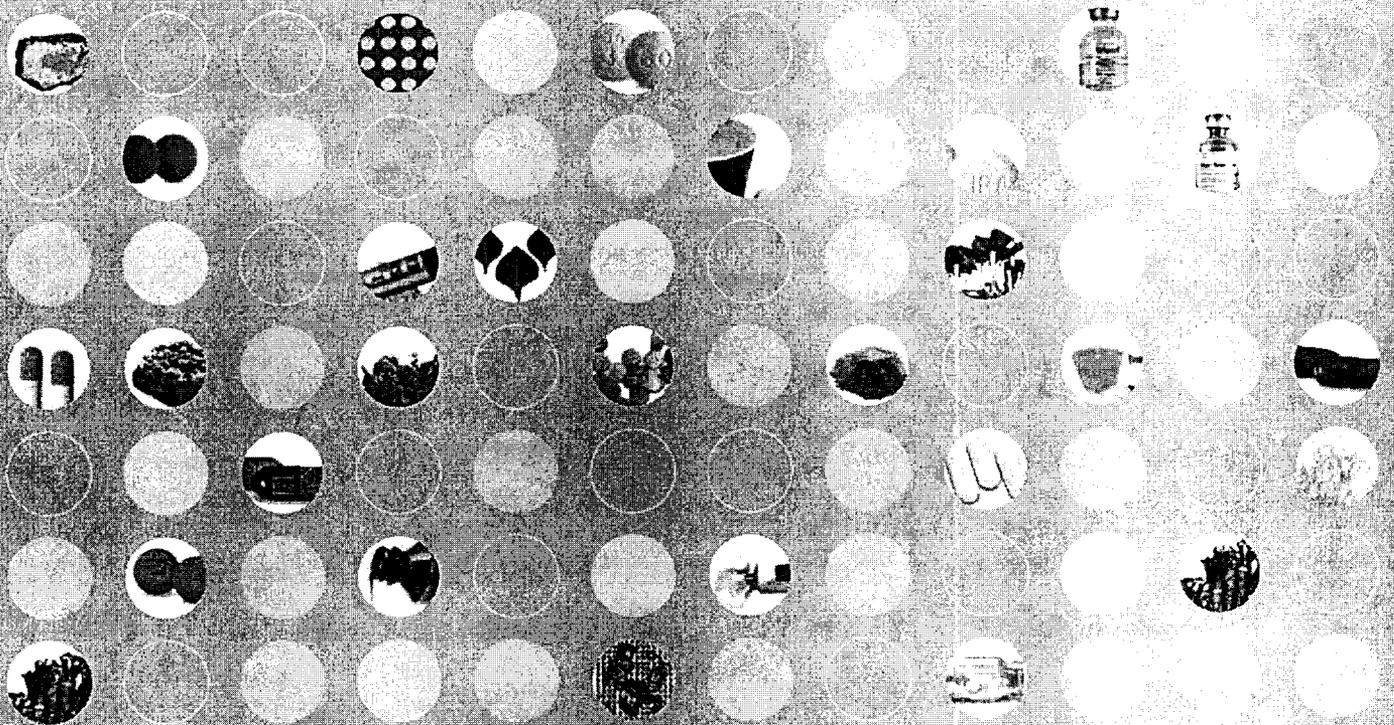
- Al-Habori, M., 2005. The potential adverse effects of habitual use of *Catha edulis* (khat). *Expert Opin. Drug. Saf.* 4, 1145–1154.
- Balint, E.E., Falkay, G., Balint, G.A., 2009. Khat—a controversial plant. *Wien. Klin. Wochenschr.* 121, 604–614.
- Brenneisen, R., Fisch, H.V., Koelbing, V., Geissshusler, S., Kalix, P., 1990. Amphetamine-like effect in humans of the khat alkaloid cathinone. *Br. J. Clin. Pharmacol.* 30, 825–828.
- Brandt, S.D., Freeman, S., Summale, H.R., Measham, F., Cole, J., 2010. Analysis of NRG "Legal highs" in the UK: identification and formation of novel cathinones. *Drug Test. Anal.* 2, 377–382.
- Centers For Disease Control and Prevention (CDC), 2011. Emergency department visits after use of a drug sold as "bath salts"—Michigan, November 13, 2010–March 31, 2011. *MMWR Morb. Mortal. Wkly. Rep.* 60, 624–627.
- Collins, M., 2011. Some new psychoactive substances: precursor chemicals and synthesis-driven and -products. *Drug Test. Anal.* 3, 404–416.

- Colzato, L.S., Ruiz, M.J., Van den Wildenberg, W.P.M., Hommel, B., 2011. Khat use is associated with impaired working memory and cognitive flexibility. *PLoS One* 6, e20602.
- Cozzi, N.V., Sievert, M.K., Shulgin, A.T., Jacob III, P., Ruoho, A.E., 1999. Inhibition plasma membrane monoamine transporters by beta-ketoamphetamines. *Eur. J. Pharmacol.* 381, 63–69.
- Dargan, P.I., Sedefov, R., Gallegos, A., Wood, D.M., 2011. The pharmacology and toxicology of the synthetic cathinone mephedrone (4-methylmethcathinone). *Drug Test. Anal.* 3, 454–463.
- Durham, M., 2011. Ivory wave: the next mephedrone? *Emerg. Med. J.* doi:10.1136/emj.2011.1129.20.
- Gibbons, S., Zloh, M., 2010. An analysis of 'legal high' mephedrone. *Bioorg. Med. Chem. Lett.* 20, 4135–4139.
- Gordons, G., Cole, J.O., 1971. Evaluation of pyrovalerone in chronically fatigued volunteers. *Curr. Ther. Res.-Clin. Exp.* 13, 631–635.
- Hadlock, G.C., Webb, K.M., McFadden, L.M., Chu, P.W., Ellison, J.D., Allen, S.C., et al., 2011. 4-Methylmethcathinone (mephedrone): neuropharmacological effects of a designer stimulant of abuse. *J. Pharmacol. Exp. Ther.* doi:10.1124/jpet.111.184119.
- Hassan, N.A., Gunaid, A.A., Murray-Lyon, I.M., 2007. Khat (*Catha edulis*): health aspects of khat chewing. *East Mediterr. Health J.* 13, 706–718. <http://www.acep.org/Content.aspx?id=77160> (visited August 14, 2011). <http://www.bluelight.ru> (visited August 17, 2011). <http://www.caymanchem.com/pdfs/10624.pdf> (visited September 29, 2011). <http://www.drugguide.us/mdpv/encyclopedia.htm#effects> (visited August 15, 2011). <http://www.drugrecognitionexpert.us/2011/02/bath-salts-mdpv/> (visited September 29, 2011). <http://www.drugs-forum.com> (visited August 17, 2011). <http://www.emcdda.europa.eu/publications/drug-profiles/khat> (visited August 11, 2011). <http://www.emcdda.europa.eu/publication/drug-profiles/synthetic-cathinones> (visited August 11, 2011). <http://www.erowid.org> (visited August 17, 2011). <http://www.iss.it/ssps/rili/cont.php?id=2056&lang=1&tipo=2> (visited August 14, 2011). <http://www.namsdl.org/documents/ACMDCathinonesReport.pdf> (visited August 14, 2011). <http://pharmacycode.com/amphepramone.html> (visited August 13, 2011). <http://pharmacycode.com/bupropion.html> (visited August 14, 2011). <http://www.pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=20111961> (visited August 14, 2011). <http://www.scribd.com/doc/57078733/Bath-Salt> (visited August 14, 2011). <http://www.sostanze.info/sites/default/files/documenti/Scheda.tecnica.MDPV.pdf> (visited August 16, 2011). <http://www.zoklet.net> (visited August 17, 2011).
- James, D., Adams, R.D., Spears, R., Cooper, G., Lupton, D.J., Thompson, J.P., et al., 2010. Clinical characteristics of mephedrone toxicity reported to the UK National Poison Information Service. *Emerg. Med. J.* 28, 686–689.
- Kalix, P., 1986. The releasing effect of the alkaloid cathinone at centre and peripheral catecholamine storage sites. *Neuropharmacology* 25, 499–501.
- Kalix, P., 1992. Cathinone, a natural amphetamine. *Pharmacol. Toxicol.* 70, 77–86.
- Kehr, J., Ichinose, F., Yoshitake, S., Gojny, M., Silvertsson, T., Nyberg, F., et al., 2011. Mephedrone compared to MDMA (ecstasy) and amphetamine rapidly increases both dopamine and serotonin levels in nucleus accumbens of awake rats. *Br. J. Pharmacol.* doi:10.1111/j.1476-5381.2011.01499.x.
- Meltzer, P.C., Butler, D., Deschamps, R., Madras, B.K., 2006. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J. Med. Chem.* 49, 1420–1432.
- Meyer, M.R., Maurer, H.H., 2010. Metabolism of designer drugs of abuse: an updated review. *Curr. Drug Metab.* 11, 468–482.
- Nencini, P., Amiconi, G., Befani, O., Abdullahi, M.A., Anania, M.C., 1984. Possible involvement of amine oxidase inhibition in the sympathetic activation by khat (*Catha edulis*) chewing in humans. *J. Ethnopharmacol.* 11, 78–86.
- Ojanpera, I.A., Heikman, P.K., Rasanen, I.J., 2011. Urine analysis of 3,4-methylenedioxypropylpyrovalerone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther. Drug. Monit.* 33, 257–263.
- Penders, T.M., Gestring, R., 2011. Hallucinatory delirium following use of MDPV: "Bath Salts". *Gen. Hosp. Psychiatry*, doi:10.1016/j.genhosppsych.2011.05.014.
- Ross, S., Peselow, E., 2009. The neurobiology of addictive disorders. *Clin. Neuropharmacol.* 32, 269–276.
- Schifano, F., Ricciardi, A., Corazza, O., Deluca, P., Davey, Z., Raffaelli, C., et al., 2010. New drugs of abuse on the web: the role of the Psychonaut Web Mapping Project. *Riv. Psichiatr.* 45, 88–93.
- Schifano, F., Albanese, A., Fergus, S., Stair, J.L., Deluca, P., Corazza, O., et al., 2011. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. *Psychopharmacology* 214, 593–602.
- Spiller, H.A., Ryan, M.L., Weston, R.G., Jansen, J., 2011. Clinical experience with analytical confirmation "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin. Toxicol.* 49, 499–505.
- Strano-rossi, S., Cadwallader, A.B., de la Torre, X., Botrè, F., 2011. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylpyrovalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun. Mass Spectrom.* 24, 2706–2714.
- Walsh, C., 2011. Drugs, the internet and change. *J. Psychoactive Drugs* 43, 55–63.
- Westphal, F., Junge, T., Rosner, P., Sonnichsen, F., Schuster, F., 2009. Mass and NMR spectroscopic characterization of 3,4-methylenedioxypropylpyrovalerone: a designer drug with alpha-pyrrolidinophenone structure. *Forensic Sci. Int.* 190, 1–8.
- Winstock, A.R., Mitcheson, L.R., Davey, Z., Corazza, O., Schifano, F., 2011. Mephedrone, new kid for the chop? *Addiction* 106, 154–161.
- Wood, D.M., Davies, S., Greene, S.L., Button, J., Holt, D.W., Ramsey, J., et al., 2010. Case series of individuals with analytically confirmed acute mephedrone toxicity. *Clin. Toxicol.* 48, 924–927.
- Yohannan, J.C., Bozenko, J.S., 2010. The characterisation of 3,4-methylenedioxypropylpyrovalerone. *Microgram J.* 7, 12–15.



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Drugs of Abuse

2011 EDITION • A DEA RESOURCE GUIDE



Drugs of Abuse



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Contents



I. Letter from Administrator	7	VII. Depressants	50
II. Controlled Substances Act	8	Barbiturates	52
Drug Scheduling	15	Benzodiazepines	53
Schedule I	15	GHB	54
Schedule II	18	Rohyphol®	56
Schedule III	20	VIII. Hallucinogens	58
Schedule IV	23	Ecstasy/MDMA	60
Schedule V	25	K2/Spice	62
Federal Trafficking Penalties	26	Ketamine	63
Federal Trafficking Penalties – Marijuana	27	LSD	65
III. U. S. Chemical Control	28	Peyote & Mescaline	66
Listed Chemicals Chart	30	Psilocybin	67
IV. Introduction to Drug Classes	32	IX. Marijuana/Cannabis	68
V. Narcotics	34	X. Steroids	70
Heroin	36	XI. Inhalants	72
Hydromorphone	37	XII. Drugs of Concern	74
Methadone	38	Bath Salts or Designer Cathinones	74
Morphine	39	DXM	76
Opium	40	Salvia Divinorum	78
Oxycodone	41	XIII. Resources	79
VI. Stimulants	42		
Amphetamines	44		
Cocaine	45		
Khat	47		
Methamphetamine	48		



WELCOME TO THE LATEST EDITION OF DRUGS OF ABUSE

The abuse of drugs is not a harmless personal decision: there are real, long-lasting, and devastating outcomes for those who abuse drugs and for their families, friends, and communities. And for some, the outcome may be lethal.

With the knowledge contained in this edition, you can make smart choices for yourself, and help others avoid the tragedy that inevitably comes from drug abuse and addiction. Whether you purchase drugs from a pharmacy, or you get them from a friend, knowing the truth about them will help you understand the dangers they pose.

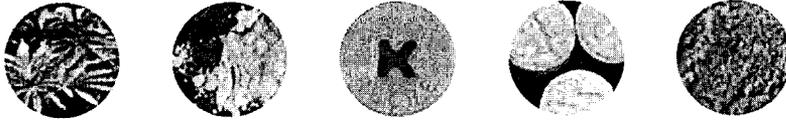
Measured in American lives, health, safety, and resources, this cost is enormous:

- » More young Americans die from drugs than suicides, firearms, or school violence;
- » The use of illicit drugs, and the non-medical use of prescription drugs, directly led to the death of 38,000 Americans in 2006, nearly as many who died in automobile accidents;
- » The only disease that affects more people than substance abuse in America today is heart disease;
- » Substance abuse is the single largest contributor to crime in the United States;
- » In the latest year measured, the direct cost of drug abuse was estimated at \$52 billion, with indirect costs of \$128 billion.

I believe none of this is necessary, and that with accurate, honest information about drugs, more Americans will make the right choices. *Drugs of Abuse* is designed to be a reliable resource on the most popularly abused drugs. This publication delivers clear, scientific information about drugs in a factual, straightforward way, combined with scores of precise photographs shot to scale. We believe that *Drugs of Abuse* fulfills an important educational need in our society.

Around the world and across the nation, the dedicated men and women of the DEA are working hard to investigate and arrest the traffickers of dangerous drugs, such as those described here. They help keep our schools and neighborhoods safe and secure. But just as important, they are working hard to educate America's youth, their parents, and their teachers about the very real dangers of illegal drugs. *Drugs of Abuse* is an important step in that direction.

Michele M. Leonhart
Administrator



II. Controlled Substances Act

CONTROLLING DRUGS OR OTHER SUBSTANCES THROUGH FORMAL SCHEDULING

The Controlled Substances Act (CSA) places all substances which were in some manner regulated under existing federal law into one of five schedules. This placement is based upon the substance's medical use, potential for abuse, and safety or dependence liability. The Act also provides a mechanism for substances to be controlled (added to or transferred between schedules) or decontrolled (removed from control). The procedure for these actions is found in Section 201 of the Act (21 U.S.C. § 811).

Proceedings to add, delete, or change the schedule of a drug or other substance may be initiated by the Drug Enforcement Administration (DEA), the Department of Health and Human Services (HHS), or by petition from any interested party, including:

- » The manufacturer of a drug
- » A medical society or association
- » A pharmacy association
- » A public interest group concerned with drug abuse
- » A state or local government agency
- » An individual citizen

When a petition is received by the DEA, the agency begins its own investigation of the drug. The DEA also may begin an investigation of a drug at any time based upon information received from law enforcement laboratories, state and local law enforcement and regulatory agencies, or other sources of information.

Once the DEA has collected the necessary data, the DEA Administrator, by authority of the Attorney General, requests from HHS a scientific and medical evaluation and recommendation as to whether the drug or other substance should be controlled or removed from control. This request is sent to the Assistant Secretary for Health of HHS.

The Assistant Secretary, by authority of the Secretary, compiles the information and transmits back to the DEA: a medical and scientific evaluation regarding the drug or other substance, a recommendation as to whether the drug should be controlled, and in what schedule it should be placed.

The medical and scientific evaluations are binding on the DEA with respect to scientific and medical matters and form a part of the scheduling decision.

Once the DEA has received the scientific and medical evaluation from HHS, the Administrator will evaluate all available data and make a final decision whether to propose that a drug or other substance should be removed or controlled and into which schedule it should be placed.

If a drug does not have a potential for abuse, it cannot be controlled. Although the term "potential for abuse" is not defined in the CSA, there is much discussion of the term in the legislative history of the Act. The following items are indicators that a drug or other substance has a potential for abuse:

- (1) There is evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.
- (2) There is significant diversion of the drug or other substance from legitimate drug channels.
- (3) Individuals are taking the drug or other substance on their own initiative rather than on the basis of medical advice from a practitioner.
- (4) The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community. Of course, evidence

of actual abuse of a substance is indicative that a drug has a potential for abuse.

In determining into which schedule a drug or other substance should be placed, or whether a substance should be decontrolled or rescheduled, certain factors are required to be considered. These factors are listed in Section 201 (c), [21 U.S.C. § 811 (c)] of the CSA as follows:

- (1) *The drug's actual or relative potential for abuse.*
- (2) *Scientific evidence of the drug's pharmacological effect, if known.* The state of knowledge with respect to the effects of a specific drug is, of course, a major consideration. For example, it is vital to know whether or not a drug has a hallucinogenic effect if it is to be controlled due to that effect.
The best available knowledge of the pharmacological properties of a drug should be considered.
- (3) *The state of current scientific knowledge regarding the substance.* Criteria (2) and (3) are closely related. However, (2) is primarily concerned with pharmacological effects and (3) deals with all scientific knowledge with respect to the substance.
- (4) *Its history and current pattern of abuse.* To determine whether or not a drug should be controlled, it is important to know the pattern of abuse of that substance.
- (5) *The scope, duration, and significance of abuse.* In evaluating existing abuse, the DEA Administrator must know not only the pattern of abuse, but whether the abuse is widespread.
- (6) *What, if any, risk there is to the public health.* If a drug creates dangers to the public health, in addition to or because of its abuse potential, then these dangers must also be considered by the Administrator.
- (7) *The drug's psychic or physiological dependence liability.* There must be an assessment of the extent to which a drug is physically addictive or psychologically habit forming.
- (8) *Whether the substance is an immediate precursor of a substance already controlled.* The CSA allows inclusion of immediate precursors on this basis alone into the appropriate schedule and thus safeguards against possibilities of clandestine manufacture. After considering the above listed factors, the Administrator must make specific findings concerning the drug or other substance. This will determine into which schedule the drug or other substance will be placed. These schedules are established by the CSA. They are as follows:

Schedule I

- » The drug or other substance has a high potential for abuse.
- » The drug or other substance has no currently accepted medical use in treatment in the United States.
- » There is a lack of accepted safety for use of the drug or other substance under medical supervision.
- » Examples of Schedule I substances include heroin, gamma hydroxybutyric acid (GHB), lysergic acid diethylamide (LSD), marijuana, and methaqualone.

Schedule II

- » The drug or other substance has a high potential for abuse.
- » The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
- » Abuse of the drug or other substance may lead to severe psychological or physical dependence.
- » Examples of Schedule II substances include morphine, phencyclidine (PCP), cocaine, methadone, hydrocodone, fentanyl, and methamphetamine.

Schedule III

- » The drug or other substance has less potential for abuse than the drugs or other substances in Schedules I and II.
- » The drug or other substance has a currently accepted medical use in treatment in the United States.
- » Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
- » Anabolic steroids, codeine and hydrocodone products with aspirin or Tylenol®, and some barbiturates are examples of Schedule III substances.

Schedule IV

- » The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.
- » The drug or other substance has a currently accepted medical use in treatment in the United States.
- » Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.
- » Examples of drugs included in Schedule IV are alprazolam, clonazepam, and diazepam.

Document released under the
Access to Information Act

Schedule V

- » The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.
- » The drug or other substance has a currently accepted medical use in treatment in the United States.
- » Abuse of the drug or other substances may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.
- » Cough medicines with codeine are examples of Schedule V drugs.

When the DEA Administrator has determined that a drug or other substance should be controlled, decontrolled, or rescheduled, a proposal to take action is published in the Federal Register. The proposal invites all interested persons to file comments with the DEA and may also request a hearing with the DEA. If no hearing is requested, the DEA will evaluate all comments received and publish a final order in the Federal Register, controlling the drug as proposed or with modifications based upon the written comments filed. This order will set the effective dates for imposing the various requirements of the CSA.

If a hearing is requested, the DEA will enter into discussions with the party or parties requesting a hearing in an attempt to narrow the issue for litigation. If necessary, a hearing will then be held before an Administrative Law Judge. The judge will take evidence on factual issues and hear arguments on legal questions regarding the control of the drug. Depending on the scope and complexity of the issues, the hearing may be brief or quite extensive. The Administrative Law Judge, at the close of the hearing, prepares findings of fact and conclusions of law and a recommended decision that is submitted to the DEA Administrator. The DEA Administrator will review these documents, as well as the underlying material, and prepare his/her own findings of fact and conclusions of law (which may or may not be the same as those drafted by the Administrative Law Judge). The DEA Administrator then publishes a final order in the Federal Register either scheduling the drug or other substance or declining to do so.

Once the final order is published in the Federal Register, interested parties have 30 days to appeal to a U.S. Court of Appeals to challenge the order. Findings of fact by the Administrator are deemed conclusive if supported by "substantial evidence." The order imposing controls is not stayed during the appeal, however, unless so ordered by the Court.

Emergency or Temporary Scheduling

The CSA was amended by the Comprehensive Crime Control Act of 1984. This Act included a provision which allows the DEA Administrator to place a substance, on a temporary basis, into Schedule I, when necessary, to avoid an imminent hazard to the public safety.

This emergency scheduling authority permits the scheduling of a substance which is not currently controlled, is being abused, and is a risk to the public health while the formal rulemaking procedures described in the CSA are being conducted. This emergency scheduling applies only to substances with no accepted medical use.

A temporary scheduling order may be issued for one year with a possible extension of up to six months if formal scheduling procedures have been initiated. The notice of intent and order are published in the Federal Register, as are the proposals and orders for formal scheduling. [21 U.S.C. § 811 (h)]

Controlled Substance Analogues

A new class of substances was created by the Anti-Drug Abuse Act of 1986. Controlled substance analogues are substances that are not controlled substances, but may be found in illicit trafficking. They are structurally or pharmacologically similar to Schedule I or II controlled substances and have no legitimate medical use. A substance that meets the definition of a controlled substance analogue and is intended for human consumption is treated under the CSA as if it were a controlled substance in Schedule I. [21 U.S.C. § 802 (32), 21 U.S.C. § 813]

International Treaty Obligations

United States treaty obligations may require that a drug or other substance be controlled under the CSA, or rescheduled if existing controls are less stringent than those required by a treaty. The procedures for these scheduling actions are found in Section 201 (d) of the Act. [21 U.S.C. § 811 (d)]

The United States is a party to the Single Convention on Narcotic Drugs of 1961, which was designed to establish effective control over international and domestic traffic in narcotics, coca leaf, cocaine, and cannabis. A second treaty, the Convention on Psychotropic Substances of 1971, which entered into force in 1976 and was ratified by Congress in 1980, is designed to establish comparable control over stimulants, depressants, and hallucinogens.

REGULATION

The CSA creates a closed system of distribution for controlled substances.

The cornerstone of this system is the registration of all those authorized by DEA to handle controlled substances. All individuals and firms that are registered are required to maintain complete and accurate inventories, and records of all transactions involving controlled substances, as well as security for the storage of controlled substances.

Registration

Any person who handles or intends to handle controlled substances must obtain a registration issued by DEA. A unique number is assigned to each legitimate handler of controlled drugs such as importer, exporter, manufacturer, distributor, hospital, pharmacy, practitioner, and researcher.

This number must be made available to the supplier by the customer prior to the purchase of a controlled substance.

Thus, the opportunity for unauthorized transactions is greatly diminished.

Recordkeeping and Reporting

The CSA requires that complete and accurate records be kept of all quantities of controlled substances manufactured, purchased, and sold. Each substance must be inventoried every two years. Some limited exceptions to the recordkeeping requirements may apply to certain categories of registrants.

From these records it is possible to trace the flow of any drug from the time it is first imported or manufactured, through the distribution level, to the pharmacy or hospital that dispensed it, and then to the actual patient who received the drug. The mere existence of this requirement is sufficient to discourage many forms of diversion. It actually serves large drug corporations as an internal check to uncover diversion, such as pilferage by employees.

There is one distinction between scheduled items for record keeping requirements. Records for Schedule I and II drugs must be kept separate from all other records maintained by the registrant. Records for Schedule III, IV, and V substances must be kept in a "readily retrievable" form, or maintained separately from all other records.

Distribution

Maintaining records is required for distribution of a controlled substance from one manufacturer to another, from manufacturer to distributor, and from distributor to dispenser. In the case of Schedule I and II drugs, the supplier must have a special order form from the customer. This order form (DEA Form 222) is issued by DEA only to persons who are properly registered to handle Schedule I and II controlled substances.

The form is preprinted with the name and address of the customer. The drugs must be shipped to this name and address. The use of this form is a special reinforcement of the registration requirement; it ensures that only authorized individuals may obtain Schedule I and II drugs.

Controlled Substance Ordering System (CSOS) – Electronic Order Forms

Any registrant permitted to order Schedule II controlled substances may do so electronically via the DEA Controlled Substance Ordering System (CSOS). The use of electronic orders is optional; registrants may continue to issue orders on a paper DEA Form 222. CSOS allows for secure electronic transmission of controlled substance orders without the supporting paper DEA Form 222. The adoption of the CSOS standards is the only allowance for the electronic transmission of Schedule II controlled substance orders between controlled substance manufacturers, distributors, pharmacies, and other DEA authorized entities. CSOS uses Public Key Infrastructure (PKI) technology, which requires CSOS users to obtain a CSOS digital certificate for electronic ordering. The electronic orders must be signed using a digital signature issued by a Certification Authority (CA) operated by DEA.

Digital certificates can be obtained only by registrants and individuals granted power of attorney by registrants to sign orders. A registrant must appoint a CSOS coordinator who will serve as that registrant's recognized agent regarding issues pertaining to issuance of, revocation of, and changes to, digital certificates issued under that registrant's DEA registration. A CSOS digital certificate will be valid until the DEA registration under which it is issued expires or until the CSOS CA is notified that the certificate should be revoked. Certificates will be revoked if the certificate holder is no longer authorized to sign Schedule II orders for the registrant, if the information on which the certificate is based changes, or if the digital certificate used to sign electronic orders has been compromised, stolen, or lost.

Another benefit of the form is the special monitoring it permits. The form is issued in triplicate: the customer keeps one copy; two copies go to the supplier, who, after filling the order, keeps a copy and forwards the third copy to the nearest DEA office. For drugs in Schedules III, IV, and V, no order form is necessary. The supplier in each case, however, is under an obligation to verify the authenticity of the customer. The supplier is held fully accountable for any drugs that are shipped to a purchaser who does not have a valid registration. Manufacturers must submit periodic reports of the Schedule I and II controlled substances they produce in bulk and dosage forms.

They also report the manufactured quantity and form of each narcotic substance listed in Schedule III. Distributors of controlled substances must report the quantity and form of all their transactions of controlled drugs listed in Schedules I and II, narcotics listed in Schedule III, and GHB. Both manufacturers and distributors are required to provide reports of their annual inventories of these controlled substances. This data is entered into a system called the Automated Reports and Consolidated Orders System (ARCOS). It enables the DEA to monitor the distribution of controlled substances throughout the country, and to identify retail level registrants that receive unusual quantities of controlled substances.

Dispensing to Patients

The dispensing of a controlled substance is the delivery by a practitioner of the controlled substance to the ultimate user, who may be a patient or research subject. Special control mechanisms operate here as well. Schedule I drugs are those that have no currently accepted medical use in the United States; therefore, they may be used in the United States only in research situations. They generally are supplied by only a limited number of firms to properly registered and qualified researchers. Controlled substances may be dispensed by a practitioner by direct administration, by prescription, or by dispensing.

Records must be maintained by the practitioner of all dispensing of controlled substances and of certain administrations. The CSA does not require the practitioner to maintain copies of prescriptions, unless, such substances are prescribed in the course of maintenance or detoxification treatment of an individual. Certain states require the use of multiple-copy prescriptions for Schedule II and other specified controlled substances.

The determination to place drugs on prescription is within the jurisdiction of the FDA. Unlike other prescription drugs, however, controlled substances are subject to additional restrictions. Schedule II prescription orders must be written and signed by the practitioner; they may not be telephoned into the pharmacy except in an emergency. In addition, a prescription for a Schedule II drug may not be refilled. For Schedule III and IV drugs, the prescription order may be either written or oral (that is, by telephone to the pharmacy). In addition, the patient may (if authorized by the practitioner) have the prescription refilled up to five times and at anytime within six months from the date the prescription was issued.

Schedule V includes some prescription drugs and many narcotic preparations, including antitussives and antidiarrheals. Even here, however, the law imposes restrictions beyond those normally required for the over-the-counter sales; for example, the patient must be at least 18 years of age, must offer some form of identification, and have his or her name entered into a special log maintained by the pharmacist as part of a special record.

Electronic Prescriptions

On March 31, 2010, DEA published in the Federal Register the *Electronic Prescriptions for Controlled Substances* interim final rule which became effective June 1, 2010. The rule provides practitioners with the option of writing prescriptions for controlled substances electronically and also permits pharmacies to receive, dispense, and archive these electronic prescriptions.

Persons who wish to dispense controlled substances using electronic prescriptions must select software that meets the requirements of this rule. As of June 1, 2010, only those electronic applications that comply with all of DEA's requirements as set forth in 21 C.F.R. §1311 may be used to electronically create, transmit, receive/archive controlled substances prescriptions, and dispense controlled substances based on those prescriptions.

Ryan Haight Online Pharmacy Consumer Protection Act of 2008

On October 15, 2008, the President signed into law the *Ryan Haight Online Pharmacy Consumer Protection Act of 2008*, often referred to as the *Ryan Haight Act*. This law amends the CSA by adding a series of new regulatory requirements and criminal provisions designed to combat the proliferation of so-called "rogue Internet sites" that unlawfully dispense controlled substances by means of the Internet. The *Ryan Haight Act* applies to all controlled substances in all schedules. An online pharmacy is a person, entity, or Internet

User Accountability/Personal Use Penalties

On November 19, 1988, Congress passed the Anti-Drug Abuse Act of 1988, P. L. 100-690. Two sections of this Act represent the U.S. Government's attempt to reduce drug abuse by dealing not just with the person who sells the illegal drug, but also with the person who buys it. The first new section is titled "User Accountability," and is codified at 21 U.S.C. § 862 and various sections of Title 42, U.S.C. The second involves "personal use amounts" of illegal drugs, and is codified at 21 U.S.C. § 844a.

User Accountability

The purpose of User Accountability is to not only make the public aware of the Federal Government's position on drug abuse, but to describe new programs intended to decrease drug abuse by holding drug abusers personally responsible for their illegal activities, and imposing civil penalties on those who violate drug laws.

It is important to remember that these penalties are in addition to the criminal penalties drug abusers are already given, and do not replace those criminal penalties.

The new User Accountability programs call for more instruction in schools, kindergarten through senior high, to educate children on the dangers of drug abuse. These programs will include participation by students, parents, teachers, local businesses and the local, state, and Federal Government.

User Accountability also targets businesses interested in doing business with the Federal Government. This program requires those businesses to maintain a drug-free workplace, principally through educating employees on the dangers of drug abuse, and by informing employees of the penalties they face if they engage in illegal drug activity on company property. There is also a provision in the law that makes public housing projects drug-free by evicting those residents who allow their units to be used for illegal drug activity, and denies federal benefits, such as housing assistance and student loans, to individuals convicted of illegal drug activity. Depending on the offense, an individual may be prohibited from ever receiving any benefit provided by the Federal Government.

Personal Use Amounts

This section of the 1988 Act allows the government to punish minor drug offenders without giving the offender a criminal record if the offender is in possession of only a small amount of drugs. This law is designed to impact the "user" of illicit

drugs, while simultaneously saving the government the costs of a full-blown criminal investigation. Under this section, the government has the option of imposing only a civil fine on individuals possessing only a small quantity of an illegal drug. Possession of this small quantity, identified as a "personal use amount," carries a civil fine of up to \$10,000.

In determining the amount of the fine in a particular case, the drug offender's income and assets will be considered. This is accomplished through an administrative proceeding rather than a criminal trial, thus reducing the exposure of the offender to the entire criminal justice system, and reducing the costs to the offender and the government.

The value of this section is that it allows the government to punish a minor drug offender, gives the drug offender the opportunity to fully redeem himself or herself, and have all public record of the proceeding destroyed. If this was the drug offender's first offense, and the offender has paid all fines, can pass a drug test, and has not been convicted of a crime after three years, the offender can request that all proceedings be dismissed.

If the proceeding is dismissed, the drug offender can lawfully say he or she had never been prosecuted, either criminally or civilly, for a drug offense.

Congress has imposed two limitations on this section's use. It may not be used if (1) the drug offender has been previously convicted of a Federal or state drug offense; or (2) the offender has already been fined twice under this section.

DRUG SCHEDULING

This document is a general reference and not a comprehensive list. This list describes the basic or parent chemical and does not describe the salts, isomers and salts of isomers, esters, ethers and derivatives which may also be controlled substances.

SCHEDULE I

NAME	DEA NUMBER	NARCOTIC	OTHER NAMES
1-(1-Phenylcyclohexyl)pyrrolidine	7458	N	PCPy, PHP, rolicyclidine
1-(2-Phenylethyl)-4-phenyl-4-acetoxypiperidine	9663	Y	PEPAP, synthetic heroin
1-[1-(2-Thienyl)cyclohexyl]piperidine	7470	N	TCP, tenocyclidine
1-[1-(2-Thienylcyclohexyl)pyrrolidine	7473	N	TCPy
1-Methyl-4-phenyl-4-propionoxypiperidine	9661	Y	MPPP, synthetic heroin
2,5-Dimethoxy-4-(n)-propylthiophenethylamine	7348	N	2C-t-7
2,5-Dimethoxy-4-ethylamphetamine	7399	N	DOE I
2,5-Dimethoxyamphetamine	7396	N	DMA, 2,5-DMA
3,4,5-Trimethoxyamphetamine	7390	N	TMA
3,4-Methylenedioxyamphetamine	7400	N	MDA, Love Drug
3,4-Methylenedioxymethamphetamine	7405	N	MDMA, Ecstasy, XTC
3,4-Methylenedioxy-N-ethylamphetamine	7404	N	N-ethyl MDA, MDE, MDEA
3-Methylfentanyl	9813	Y	China White, fentanyl
3-Methylthiofentanyl	9833	Y	China White, fentanyl
4-Bromo-2,5-dimethoxyamphetamine	7391	N	DOB, 4-bromo-DMA
4-Bromo-2,5-dimethoxyphenethylamine	7392	N	Nexus, 2-CB, has been sold as Ecstasy, i.e. MDMA
4-Methoxyamphetamine	7411	N	PMA
4-Methyl-2,5-dimethoxyamphetamine	7395	N	DOM, STP
4-Methylaminorex (cis isomer)	1590	N	U4Euh, McN-422
5-Methoxy-3,4-methylenedioxyamphetamine	7401	N	MMDA
5-Methoxy-N,N-diisopropyltryptamine	7439	N	5-MeO-DIPT
Acetorphine	9319	Y	
Acetyl-alpha-methylfentanyl	9815	Y	
Acetyldihydrocodeine	9051	Y	Acetylcodeine
Acetylmethadol	9601	Y	Methadyl acetate
Allylprodine	9602	Y	
Alphacetylmethadol except levo-alphacetylmethadol	9603	Y	
Alpha-Ethyltryptamine	7249	N	FT, Trip
Alphameprodine	9604	Y	
Alphamethadol	9605	Y	
Alpha-Methylfentanyl	9814	Y	China White, fentanyl
Alpha-Methylthiofentanyl	9832	Y	China White, fentanyl
Alpha-methyltryptamine	7432	N	AMT
Aminorex	1585	N	has been sold as methamphetamine
Benzethidine	9606	Y	
Benzylmorphine	9052	Y	
Betacetylmethadol	9607	Y	

SCHEDULE I

DESCRIPTION	DEA NUMBER	NARCOTIC	OTHER NAMES
Beta-hydroxy-3-methylfentanyl	9831	Y	China White, fentanyl
Beta-hydroxyfentanyl	9830	Y	China White, fentanyl
Betameprodine	9608	Y	
Betamethadol	9609	Y	
Betaprodine	9611	Y	
Bufotenine	7433	N	Mappine, N,N-dimethylserotonin
Cathinone	1235	N	Constituent of "Khat" plant
Clonitazene	9612	Y	
Codeine methylbromide	9070	Y	
Codeine-N-oxide	9053	Y	
Cyprenorphine	9054	Y	
Desomorphine	9055	Y	
Dextromoramide	9613	Y	Palfium, Jetrium, Narcolo
Diampromide	9615	Y	
Diethylthiambutene	9616	Y	
Diethyltryptamine	7434	N	DET
Difenoxin	9168	Y	Lyspafen
Dihydromorphine	9145	Y	
Dimenoxadol	9617	Y	
Dimepheptanol	9618	Y	
Dimethylthiambutene	9619	Y	
Dimethyltryptamine	7435	N	DMT
Dioxaphetyl butyrate	9621	Y	
Dipipanone	9622	Y	Dipipan, phenylpiperone HCl, Diconal, Wellconal
Drotebanol	9335	Y	Metebanyl, oxymethebanol
Ethylmethylthiambutene	9623	Y	
Etonitazene	9624	Y	
Etorphine (except HCl)	9056	Y	
Etoxidine	9625	Y	
Fenethylamine	1503	N	Captagon, amfetamine, ethyltheophylline, amphetamine
Furethidine	9626	Y	
Gamma Hydroxybutyric Acid	2010	N	GHB, gamma hydroxybutyrate, sodium oxybate
Heroin	9200	Y	Diacetylmorphine, diarmorphine
Hydromorphone	9301	Y	
Hydroxypethidine	9627	Y	
Ibogaine	7260	N	Constituent of "Tabernanthe iboga" plant
Ketobemidone	9628	Y	Cliradon
Levomoramide	9629	Y	
Levophenacymorphan	9631	Y	
Lysergic acid diethylamide	7315	N	LSD, lysergide

SCHEDULE I

SUBSTANCE	DEA NUMBER	NARCOTICS	OTHER NAMES
Marijuana	7360	N	Cannabis, marijuana
Medoqualone	2572	N	Nubarone
Mescaline	7381	N	Constituent of "Peyote" cacti
Methaqualone	2565	N	Quaalude, Farest, Somnafac, Opitimid, Mandrax
Methcathinone	1237	N	N-Methylcathinone, "cat"
Methyldesorphine	9302	Y	
Methyldihydromorphine	9304	Y	
Morphendine	9632	Y	
Morphine methylbromide	9305	Y	
Morphine methylsulfonate	9306	Y	
Morphine-N-oxide	9307	Y	
Myrophine	9308	Y	
N,N-Dimethylamphetamine	1480	N	
N-Benzylpiperazine	7493	N	BZP, 1-benzylpiperazine
N-Ethyl-1-phenylcyclohexylamine	7455	N	PCE
N-Ethyl-3-piperidyl benzilate	7482	N	JB 323
N-Ethylamphetamine	1475	N	NEA
N-Hydroxy-3,4-methylenedioxyamphetamine	7402	N	N-hydroxy MDA
Nicocodeine	9309	Y	
Nicomorphine	9312	Y	Vilan
N-Methyl-3-piperidyl benzilate	7484	N	JB 336
Noracymethadol	9633	Y	
Norlevorphanol	9634	Y	
Normethadone	9635	Y	Phenyldimazone
Normorphine	9313	Y	
Norpipanone	9636	Y	
Para-Fluorofentanyl	9812	Y	China White, fentanyl
Parahexyl	7374	N	Synhexyl
Peyote	7415	N	Cactus which contains mescaline
Phenadoxone	9637	Y	
Phenampromide	9638	Y	
Phenomorphin	9647	Y	
Phenopendine	9641	Y	Operidine, Lealgin
Pholcodine	9314	Y	Copholco, Adaphol, Codisol, Lantuss, Pholcolin
Piritramide	9642	Y	Piridolan
Proheptazine	9643	Y	
Properidine	9644	Y	
Propiram	9649	Y	Algeril
Psilocybin	7437	N	Constituent of "Magic mushrooms"
Psilocyn	7438	N	Psilocin, constituent of "Magic mushrooms"

SCHEDULE I

SUBSTANCE	DEA NUMBER	NARCOTIC	OTHER NAMES
Racemoramide	9645	Y	
Tetrahydrocannabinols	7370	N	THC, Delta-8 THC, Delta-9 THC, dronabinol and others
Thebacon	9315	Y	Acetylhydrocodone, Acedicon, Thebacetyl
Thiofentanyl	9835	Y	Chine white, fentanyl
Tilidine	9750	Y	Tilidate, Valoron, Kitadol, Lak, Tilsa
Trimeperidine	9646	Y	Promedolum

SCHEDULE II

SUBSTANCE	DEA NUMBER	NARCOTIC	OTHER NAMES
1-Phenylcyclohexylamine	7460	N	Precursor of PCP
1-Piperidinocyclohexanecarbonitrile	8603	N	PCC, precursor of PCP
4-Anilino-N-phenethyl-4-piperidine (ANPP)	8333	N	ANPP
Alfentanil	9737	Y	Alfenta
Alphaprodine	9010	Y	Nisentil
Amobarbital	2125	N	Amytal, Tuinal
Amphetamine	1100	N	Dexedrine, Adderall, Obetrol
Anileridine	9020	Y	Leritine
Benzoylcegonine	9180	Y	Cocaine metabolite
Bezitamide	9800	Y	Burgodin
Carfentanil	9743	Y	Wildnil
Coca Leaves	9040	Y	
Cocaine	9041	Y	Methyl benzoylcegonine, Crack
Codeine	9050	Y	Morphine methyl ester, methyl morphine
Dextropropoxyphene, bulk (non-dosage forms)	9273	Y	Propoxyphene
Dihydrocodeine	9120	Y	Didrate, Parzone
Dihydroetorphine	9334	Y	DHE
Diphenoxylate	9170	Y	
Diprenorphine	9058	Y	M50-50
Ecgonine	9180	Y	Cocaine precursor, in Coca leaves
Ethylmorphine	9190	Y	Dionin
Etorphine	9059	Y	M 99
Fentanyl	9801	Y	Duragesic, Oralet, Actiq, Sublimaze, Innovar
Glutethimide	2550	N	Doriden, Dorimide
Hydrocodone	9193	Y	dihydrocodeinone
Hydromorphone	9150	Y	Dilaudid, dihydromorphinone
Isomethadone	9226	Y	Isoamidone
Levo-alphaacetylmethadol	9648	Y	L-AAM, long acting methadone, levomethadyl acetate

SCHEDULE II

Substance	Number	Controlled	Other Name(s)
Levomethorphan	9210	Y	
Levorphanol	9220	Y	Levo-Dromoran
Lisdexamfetamine	1205	N	Vyvan
Meperidine	9230	Y	Demerol, Mepergan, pethidine
Meperidine intermediate-A	9232	Y	Meperidine precursor
Meperidine intermediate-B	9233	Y	Meperidine precursor, normeperidine
Meperidine intermediate-C	9234	Y	Meperidine precursor
Metazocine	9240	Y	
Methadone	9250	Y	Dolophine, Methadose, Amidone
Methadone intermediate	9254	Y	Methadone precursor
Methamphetamine	1105	N	Desoxyn, D-desoxyephedrine, ICE, Crank, Speed
Methylphenidate	1724	N	Concerta, Ritalin, Methylin
Metopon	9260	Y	
Moramide-intermediate	9802	Y	
Morphine	9300	Y	MS Contin, Roxanol, Oramorph, RMS, MSIR
Nabilone	7379	N	Cesamet
Opium extracts	9610	Y	
Opium fluid extract	9620	Y	
Opium poppy	9650	Y	Papaver somniferum
Opium tincture	9630	Y	Laudanum
Opium, granulated	9640	Y	Granulated opium
Opium, powdered	9639	Y	Powdered Opium
Opium, raw	9600	Y	Raw opium, gum opium
Oripavine	9330	Y	
Oxycodone	9143	Y	OxyContin, Percocet, Endocet, Roxicodone, Roxicet
Oxymorphone	9652	Y	Numorphan
Pentobarbital	2270	N	Nembutal
Phenazocine	9715	Y	Narphen, Prinadol
Phencyclidine	7471	N	PCP, Sernylan
Phenmetrazine	1631	N	Preludin
Phenylacetone	8501	N	P2P, phenyl-2-propanone, benzyl methyl ketone
Piminodine	9730	Y	
Poppy Straw	9650	Y	Opium poppy capsules, poppy heads
Poppy Straw Concentrate	9670	Y	Concentrate of Poppy Straw, CPS
Racemethorphan	9732	Y	
Racemorphan	9733	Y	Dromoran
Remifentanil	9739	Y	Ultiva
Secobarbital	2315	N	Secoral, Tuinal
Sufentanil	9740	Y	Sufenta
Tapentadol	9780	Y	
Thebaine	9333	Y	Precursor of many narcotics

SCHEDULE III

SUBSTANCE	DETAILED DESCRIPTION	DETAILED DESCRIPTION	DETAILED DESCRIPTION	DETAILED DESCRIPTION
13Beta-ethyl-17beta-hydroxygon-4-en-3-one	4000	N		
17Alpha-methyl-3alpha,17beta-dihydroxy-5alphaandrostane	4000	N		
17Alpha-methyl-3beta,17beta-dihydroxy-5alphaandrostane	4000	N		
17Alpha-methyl-3beta,17beta-dihydroxyandrost-4-ene	4000	N		
17Alpha-methyl-4-hydroxynandrolone (17alpha-methyl-4-hydroxy-17beta-hydroxyestr-4-en-3-one)	4000	N		
17Alpha-methyl-delta1-dihydrotestosterone (17beta-hydroxy-17alpha-methyl-5alpha-androst-1-en-3-one)	4000	N		17-Alpha-methyl-1-testosterone
19-Nor-4,9(10)-androstadienedione	4000	N		
19-Nor-4-androstenediol (3beta,17beta-dihydroxyestr-4-ene; 3alpha,17beta-dihydroxyestr-4-ene)	4000	N		
19-Nor-4-androstenedione (estr-4-en-3,17-dione) 4000 III N	4000	N		
19-Nor-5-androstenediol (3beta,17beta-dihydroxyestr-5-ene; 3alpha,17beta-dihydroxyestr-5-ene)	4000	N		
19-Nor-5-androstenedione (estr-5-en-3,17-dione)	4000	N		
1-Androstenediol (3beta,17beta-dihydroxy-5alphaandrost-1-ene; 3alpha,17beta-dihydroxy-5alphaandrost-1-ene)	4000	N		
1-Androstenedione (5alpha-androst-1-en-3,17-dione)	4000	N		
3Alpha,17beta-dihydroxy-5alpha-androstane	4000	N		
3Beta,17beta-dihydroxy-5alpha-androstane	4000	N		
4-Androstenediol (3beta,17beta-dihydroxy-androst-4-ene)	4000	N		4-AD
4-Androstenedione (androst-4-en-3,17-dione)	4000	N		
4-Dihydrotestosterone (17beta-hydroxyandrost-4-en-3-one)	4000	N		Anabolex, Andractim, Pesomax, Stanolone
4-Hydroxy-19-nortestosterone (4,17beta-dihydroxyestr-4-en-3-one)	4000	N		
4-Hydroxytestosterone (4,17beta-dihydroxyandrost-4-en-3-one)	4000	N		
5-Androstenediol (3beta,17beta-dihydroxy-androst-5-ene)	4000	N		
5-Androstenedione (androst-5-en-3,17-dione)	4000	N		
Amobarbital & noncontrolled active ingred.	2126	N		
Amobarbital suppository dosage form	2126	N		
Anabolic steroids	4000	N		Body Building drugs
Androstenedione (5alpha-androstan-3,17-dione)	4000	N		
Aprobarbital	2100	N		Alurate
Barbitonic acid derivative	2100	N		Barbiturates not specifically listed
Benzphetamine	1228	N		Didrex, Inapetyl
Bolasterone (3alpha,17alpha-dimethyl-17beta-hydroxyandrost-4-en-3-one)	4000	N		
Boldenone (17beta-hydroxyandrost-1,4-diene-3-one)	4000	N		Equipoise, Parenabol, Vebonol, dehydrotosterone
Boldione	4000	N		
Buprenorphine	9064	Y		Buprenex, Temgesic, Subutex, Suboxone
Butabarbital (secbutabarbital)	2100	N		Butisol, Butibel
Butalbital	2100	N		Fiorinal, Butalbital with aspirin

SCHEDULE III

Chemical Name	Control Number	Pharmaceutical	Other Name(s)
Butobarbital (butethal)	2100	N	Soneryl (UK)
Calusterone (7beta,17alpha-dimethyl-17betahydroxyandrost-4-en-3-one)	4000	N	Methosarb
Chlorhexadol	2510	N	Mechloral, Mecoral, Medodorm, Chloralodol
Chlorphentermine	1645	N	Pre-Sate, Lucofen, Apsedon, Desopimon
Clortermine	1647	N	Voranil
Clostebol (4-chloro-17beta-hydroxyandrost-4-en-3-one)	4000	N	Alfa-Trofodemin, Clostene, 4-chlorotestosterone
Codeine & isoquinoline alkaloid 90 mg/du	9803	Y	Codeine with papaverine or noscapine
Codeine combination product 90 mg/du	9804	Y	Empirin, Fiorinal, Tylenol, ASA or APAP w/ codeine
Dehydrochloromethyltestosterone (4-chloro-17betahydroxy-17alpha-methylandrost-1,4-dien-3-one)	4000	N	Oral-Turnabol
Delta1-dihydrotestosterone (17beta-hydroxy-Salphaandrost-1-en-3-one)	4000	N	1-Testosterone
Desoxymethyltestosterone	4000	N	
Dihydrocodeine combination product 90 mg/du	9807	Y	Synalgos-DC, Compal
Dronabinol (synthetic) in sesame oil in soft gelatin capsule as approved by FDA	7369	N	Marinol, synthetic THC in sesame oil/soft gelatin as approved by FDA
Drostanolone (17beta-hydroxy-2alpha-methyl-Salphaandrost-3-one)	4000	N	Drolban, Masterid, Permastril
Embutramide	2020	N	Tributane
Ethylestrenol (17alpha-ethyl-17beta-hydroxyestr-4-ene)	4000	N	Maxibolin, Orabolin, Durabolin-O, Duraboral
Ethylmorphine combination product 15 mg/du	9808	Y	
Fluoxymesterone (9-fluoro-17alpha-methyl-11beta,17beta-dihydroxyandrost-4-en-3-one)	4000	N	Anadroid-F, Halotestin, Ora-Testryl
Formebolone (2-formyl-17alpha-methyl-11alpha,17beta-dihydroxyandrost-1,4-dien-3-one)	4000	N	Escifene, Hubernol
Furazabol (17alpha-methyl-17betahydroxyandrostano[2,3-c]-furan)	4000	N	Frazalon, Miotolon, Gu Zhi Shu
Gamma Hydroxybutyric Acid preparations	2012	N	Xyrem
Hydrocodone & isoquinoline alkaloid <15 mg/du	9805	Y	Dihydrocodeinone+ papaverine or noscapine
Hydrocodone combination product <15 mg/du	9806	Y	Lorcet, Lortab, Vicodin, Vicoprofen, Tussionex, Norco
Ketamine	7285	N	Ketaset, Ketalar, Special K, K
Lysergic acid	7300	N	LSD precursor
Lysergic acid amide	7310	N	LSD precursor
Mestanolone (17alpha-methyl-17beta-hydroxy-Salphaandrost-3-one)	4000	N	Assimil, Erialone, Methybol, Tantarone
Mesterolone (1alpha-methyl-17beta-hydroxy-Salphaandrost-3-one)	4000	N	Androvron, Proviron, Testiwop
Methandienone (17alpha-methyl-17betahydroxyandrost-1,4-diene-3-one)	4000	N	Dianabol, Metabolina, Nerobol, Perbolin
Methandriol (17alpha-methyl-3beta,17betadihydroxyandrost-5-ene)	4000	N	Sinesex, Stenediol, Troformone

SCHEDULE III

Substance	Identification Number	Controlled	Trade Name
Methenolone (1-methyl-17beta-hydroxy-5alpha-androst-1-en-3-one)	4000	N	Primobolan, Primobolan Depot, Primobolan S
Methylcienolone (17alpha-methyl-17beta-hydroxyestr-4,9(10)-dien-3-one)	4000	N	
Methyltestosterone (17alpha-methyl-17betahydroxyandrost-4-en-3-one)	4000	N	Android, Oreton, Testred, Virilon
Methyltrienolone (17alpha-methyl-17beta-hydroxyestr-4,9,11-trien-3-one)	4000	N	Metribolone
Methypirylon	2575	N	Noludar
Mibolerone (7alpha,17alpha-dimethyl-17betahydroxyestr-4-en-3-one)	4000	N	Cheque, Matenon
Morphine combination product/50 mg/100 ml or gm	9810	Y	
Nalorphine	9400	Y	Naline
Nandrolone (17beta-hydroxyestr-4-en-3-one)	4000	N	Deca-Durabolin, Durabolin, Durabolin-50
Norbolethone (13beta,17alpha-diethyl-17betahydroxygon-4-en-3-one)	4000	N	Genabol
Norclostebol (4-chloro-17beta-hydroxyestr-4-en-3-one)	4000	N	Anabol-4-19, Lentabol
Norethandrolone (17alpha-ethyl-17beta-hydroxyestr-4-en-3-one)	4000	N	Nilevar, Pronabol, Solevar
Normethandrolone (17alpha-methyl-17betahydroxyestr-4-en-3-one)	4000	N	Lutenin, Matronal, Orgasteron
Opium combination product 25 mg/du	9809	Y	Paregoric, other combination products
Oxandrolone (17alpha-methyl-17beta-hydroxy-2-oxa-5alpha-androstan-3-one)	4000	N	Anavar, Lonavar, Oxandrin, Provitar, Vasorome
Oxymesterone (17alpha-methyl-4,17betahydroxyandrost-4-en-3-one)	4000	N	Anamidol, Balnimax, Oranabol, Oranabol 10
Oxymetholone (17alpha-methyl-2-hydroxymethylene-17beta-hydroxy-5alpha-androstan-3-one)	4000	N	Anadrol-50, Adroyd, Anapolon, Anasteron, Pardroyd
Pentobarbital & noncontrolled active ingred.	2271	N	FP-3
Pentobarbital suppository dosage form	2271	N	WANS
Phendimetrazine	1615	N	Plegine, Preku-2, Bontril, Melfiat, Statobex
Secobarbital & noncontrolled active ingred	2316	N	
Secobarbital suppository dosage form	2316	N	
Stanozolol (17alpha-methyl-17beta-hydroxy-5alphaandrost-2-eno[3,2-c]-pyrazole)	4000	N	N Winstrol, Winstrol-V
Stenbolone (17beta-hydroxy-2-methyl-5alpha-androst-1-en-3-one)	4000	N	
Stimulant compounds previously excepted	1405	N	Mediatric
Sulfoethylethylmethane	2600	N	
Sulfonethylmethane	2605	N	
Sulfonmethane	2610	N	
Talbutal	2100	N	Lotusate
Testolacrone (13-hydroxy-3-oxo-13,17-secoandrosta-1,4-dien-17-oiic acid lactone)	4000	N	Teclit, Teslac

SCHEDULE III

SUBSTANCE	DEA NUMBER	NARCOTIC	OTHER NAMES
Testosterone (17beta-hydroxyandrost-4-en-3-one)	4000	N	Android-E, Androlan, Depotest, Delatestyl
Tetrahydrogestrinone (13beta,17alpha-diethyl-17beta-hydroxygon-4,9,11-trien-3-one)	4000	N	THG
Thiamylal	2100	N	Sun'al
Thiopental	2100	N	Pentothal
Tiletamine & Zolazepam Combination Product	2295		Telszol
Irenbolone (17beta-hydroxyestr-4,9,11-trien-3-one)	4000	N	Finaplix-S, Finajet, Parabolan
Vinbarbital	2100	N	Delvinal, vinbarbitone

SCHEDULE IV

SUBSTANCE	DEA NUMBER	NARCOTIC	OTHER NAMES
Alprazolam	2882	N	Xanax
Barbital	2145	N	Veronal, Plexonal, barbitone
Bromazepam	2748	N	Lexotan, Lexatin, Lexotanil
Butorphanol	9720	N	Stadol, Stadol NS, Torbugesic, Torbutrol
Camazepam	2749	N	Albego, Limpidon, Paxor
Cathine	1230	N	Constituent of "Khat" plant, (+)-norpseudoephedrine
Chloral betaine	2460	N	Beta Chlor
Chloral hydrate	2465	N	Noctec
Chlordiazepoxide	2744	N	Librium, Libritabs, Limbitrol, SK-Lygen
Clobazam	2751	N	Urbadan, Urbanyl
Clonazepam	2737	N	Klonopin, Clonopin
Clorazepate	2768	N	Tranxene
Clotiazepam	2752	N	Trecalmo, Rize, Clozan, Veratran
Clozapolam	2753	N	Akton, Lubalix, Olcadil, Sepazon
Delorazepam	2754	N	
Dexfenfluramine	1670	N	Redux
Dextropropoxyphene dosage forms	9278	Y	Darvon, propoxyphene, Darvocet, Propacet
Diazepam	2765	N	Valium, Diastat
Dichloralphenazone	2467	N	Midrin, dichloralantipyrine
Diethylpropion	1610	N	Tenuate, Toponil
Difenoxin 1 mg/25 ug AtSO4/du	9167	Y	Motofen
Estazolam	2756	N	ProSom, Dominamid, Eurodin, Nuctalon
Ethchlorvynol	2540	N	Placidyl
Ethinamate	2545	N	Valmid, Valamin
Ethyl loflazepate	2758	N	
Fencamfamin	1760	N	Reactivan
Fenfluramine	1670	N	Pondimin, Ponderal
Fenproporex	1571	N	Gacilin, Solvolip
Fludiazepam	2759	N	

SCHEDULE IV

Substance	Number	Category	Trade Name
Flunitrazepam	2763	N	Rohypnol, Narcozep, Darkene, Roipnol
Flurazepam	2767	N	Dalmane
Fospropofol	2138	N	Lusedra
Halazepam	2762	N	Paxipam
Haloxazolam	2771	N	
Ketazolam	2772	N	Anxon, Loftan, Solatran, Contamex
Loprazolam	2773	N	
Lorazepam	2885	N	Ativan
Lormetazepam	2774	N	Noctamid
Mazindol	1605	N	Sanorex, Mazanor
Mebutamate	2800	N	Capla
Medazepam	2836	N	Nobrium
Mefenorex	1580	N	Anorexic, Amexate, Doracil, Pondinil
Meprobamate	2820	N	Miltown, Ecuamil, Deprol, Equagesic, Meprospan
Methohexital	2264	N	Brevital
Methylphenobarbital (mephobarbital)	2250	N	Mebaral, mephobarbital
Midazolam	2884	N	Versed
Modafinil	1680	N	Provigil
Nimetazepam	2837	N	Erimin
Nitrazepam	2834	N	Mogadon
Nordiazepam	2838	N	Nordazepam, Demadar, Madar
Oxazepam	2835	N	Serax, Serenid-D
Oxazolam	2839	N	Serenal, Convortal
Paraldehyde	2585	N	Paral
Pemoline	1530	N	Cylert
Pentazocine	9709	N	Talwin, Talwin NX, Talacen, Talwin Compound
Petrichloral	2591	N	Pentaerythritol chloral, Peridor
Phenobarbital	2285	N	Luminal, Donnatal, Bellergal-S
Phentermine	1640	N	Ionamin, Fastin, Adipex-P, Obe-Nix, Zentryl
Pinazepam	2883	N	Domar
Pipradrol	1750	N	Detari, Stimolag Fortis
Prazepam	2764	N	Centrax
Quazepam	2881	N	Doral
Sibutramine	1675	N	Meridia
SPA	1635	N	1-dimethylamino-1,2-diphenylethane, Lofetamine
Temazepam	2925	N	Restonil
Tetrazepam	2886	N	Myolastan, Musaril
Triazolam	2887	N	Halcion
Zaleplon	2781	N	Sonata
Zolpidem	2783	N	Ambien, Ivadal, Stilnoct, Stilnox

SCHEDULE V

Drug Name	Quantity	Controlled	Examples
Codeine preparations	200 mg/100 ml or 100 gm	Y	Cosanyl, Robitussin AC, Cheracol, Cerase, Pediacof
Difenoxin preparations	0.5 mg/25 ug AtSO ₄ /du	Y	Motofen
Dihydrocodeine preparations	10 mg/100 ml or 100 gm	Y	Cophene-S, various others
Diphenoxylate preparations	2.5 mg/25 ug AtSO ₄	Y	Lomotil, Logen
Ethylmorphine preparations	100 mg/100 ml or 100 gm	Y	
Lacosamide	2746	N	Vimpat
Opium preparations	100 mg/100 ml or gm	Y	Parepectolin, Kapectolin PG, Kaolin Pectin P.G.
Pregabalin	2782	N	Lyrica
Pyrovalerone	1485	N	Centroton, Thymergix

FEDERAL TRAFFICKING PENALTIES

Drug	Quantity	Penalty	Quantity	Penalty
Cocaine (Schedule II)	500 - 4999 gms mixture	First Offense: Not less than 5 yrs, and not more than 40 yrs. If death or serious injury, not less than 20 or more than life. Fine of not more than \$5 million if an individual, \$25 million if not an individual. Second Offense: Not less than 10 yrs, and not more than life. If death or serious injury, life imprisonment. Fine of not more than \$8 million if an individual, \$50 million if not an individual.	5 kgs or more mixture	First Offense: Not less than 10 yrs, and not more than life. If death or serious injury, not less than 20 or more than life. Fine of not more than \$10 million if an individual, \$50 million if not an individual. Second Offense: Not less than 20 yrs, and not more than life. If death or serious injury, life imprisonment. Fine of not more than \$20 million if an individual, \$75 million if not an individual. 2 or More Prior Offenses: Life imprisonment.
Cocaine Base (Schedule II)	28-279 gms mixture		280 gms or more mixture	
Fentanyl (Schedule II)	40 - 399 gms mixture		400 gms or more mixture	
Fentanyl Analogue (Schedule I)	10 - 99 gms mixture		100 gms or more mixture	
Heroin (Schedule I)	100 - 999 gms mixture		1 kg or more mixture	
LSD (Schedule I)	1 - 9 gms mixture		10 gms or more mixture	
Methamphetamine (Schedule II)	5 - 49 gms pure or 50 - 499 gms mixture		50 gms or more pure or 500 gms or more mixture	
PCP (Schedule II)	10 - 99 gms pure or 100 - 999 gms mixture		100 gm or more pure or 1 kg or more mixture	
Other Schedule I & II drugs (and any drug product containing Gamma Hydroxybutyric Acid)	Any amount	First Offense: Not more than 20 yrs. If death or serious injury, not less than 20 yrs, or more than life. Fine \$1 million if an individual, \$5 million if not an individual. Second Offense: Not more than 30 yrs. If death or serious injury, not more than 15 yrs. Fine \$2 million if an individual, \$10 million if not an individual.		
Other Schedule III drugs	Any amount	First Offense: Not more than 10 years. If death or serious injury, not more than 15 yrs. Fine not more than \$500,000 if an individual, \$2.5 million if not an individual. Second Offense: Not more than 20 yrs. If death or serious injury, not more than 30 yrs. Fine not more than \$1.5 million if an individual, \$5 million if not an individual.		
All other Schedule IV drugs	Any amount	First Offense: Not more than 5 years. Fine not more than \$250,000 if an individual, \$1 million if not an individual. Second Offense: Not more than 10 yrs. Fine not more than \$500,000 if an individual, \$2 million if not an individual.		
Flunitrazepam (Schedule IV)	Less than 1 gm			
All Schedule V drugs	Any amount	First Offense: Not more than 1 yr. Fine not more than \$100,000 if an individual, \$250,000 if not an individual. Second Offense: Not more than 4 yrs. Fine not more than \$200,000 if an individual, \$500,000 if not an individual.		

FEDERAL TRAFFICKING PENALTIES — MARIJUANA

OFFENSE	QUANTITIES	MINIMUM PENALTY	MAXIMUM PENALTY
Marijuana (Schedule I)	1,000 kg or more mixture; or 1,000 or more plants	<ul style="list-style-type: none"> • Not less than 10 years, not more than life • If death or serious injury, not less than 20 years, not more than life • Fine not more than \$4 million if an individual, \$10 million if other than an individual 	<ul style="list-style-type: none"> • Not less than 20 years, not more than life • If death or serious injury, mandatory life • Fine not more than \$8 million if an individual, \$20 million if other than an individual
Marijuana (Schedule I)	100 kg to 999 kg mixture; or 100 to 999 plants	<ul style="list-style-type: none"> • Not less than 5 years, not more than 40 years • If death or serious injury, not less than 20 years, not more than life • Fine not more than \$2 million if an individual, \$5 million if other than an individual 	<ul style="list-style-type: none"> • Not less than 10 years, not more than life • If death or serious injury, mandatory life • Fine not more than \$4 million if an individual, \$10 million if other than an individual
Marijuana (Schedule I)	More than 10 kgs hashish; 50 to 99 kg mixture More than 1 kg of hashish oil; 50 to 99 plants	<ul style="list-style-type: none"> • Not more than 20 years • If death or serious injury, not less than 20 years, not more than life • Fine \$1 million if an individual, \$5 million if other than an individual 	<ul style="list-style-type: none"> • Not more than 30 years • If death or serious injury, mandatory life • Fine \$2 million if an individual, \$10 million if other than individual
Marijuana (Schedule I)	1 to 49 plants; less than 50 kg	<ul style="list-style-type: none"> • Not more than 5 years 	<ul style="list-style-type: none"> • Not more than 10 years
Hashish (Schedule I)	10 kg or less	<ul style="list-style-type: none"> • Fine not more than \$250,000, \$1 million other than individual 	<ul style="list-style-type: none"> • Fine \$500,000 if an individual, \$2 million if other than individual
Hashish Oil (Schedule I)	1 kg or less		

*The minimum sentence for a violation after two or more prior convictions for a felony drug offense have become final is a mandatory term of life imprisonment without release and a fine up to \$8 million if an individual and \$20 million if other than an individual.



III. U.S. Chemical Control

The Drug Enforcement Administration (DEA) employs a multi-faceted approach to combat drug trafficking which includes enforcement, interdiction, and education. A lesser known approach which combines elements from all three of these facets is chemical control. Large quantities of chemicals are required to synthesize, extract, and purify most illicit drugs. The DEA has long recognized the need to monitor these chemicals as part of its overall drug control strategy.

During the 1980's there was a tremendous increase in the clandestine production of controlled substances, particularly methamphetamine. There was also a proliferation of clandestine laboratories producing controlled substance analogues, very potent and dangerous variations of controlled narcotics, stimulants, and hallucinogens. Furthermore, DEA learned that U.S. firms were exporting large quantities of chemicals, such as acetone, methylethylketone, and potassium permanganate to cocaine producing countries. Significant amounts of these chemicals ultimately were diverted to clandestine cocaine laboratories. It became clear that mandatory controls were needed to control the distribution of these chemicals in order to have an impact on the clandestine laboratory problem.

DEA embarked upon a broad chemical control program in 1989 that began with the Chemical Diversion and Trafficking Act (CDTA) of 1988. The CDTA regulated 12 precursor chemicals, eight essential chemicals, tableting machines and encapsulating machines by imposing recordkeeping and import/export reporting requirements on transactions involving these products. It resulted in effectively reducing the supply of illicit methamphetamine. The number of clandestine laboratories seized in the first three years following the law's implementation reversed the trend of the previous three decades and resulted in a decline. Currently, DEA

monitors 41 chemicals which are commonly used in illicit drug production. Maintaining this success requires continuous effort to thwart traffickers' never-ending search for new methods of diversion and new precursor materials.

The foundation of the government's program to prevent chemical diversion is based on additional laws such as the Domestic Chemical Diversion Control Act of 1993 (DCDCA), the Comprehensive Methamphetamine Control Act of 1996 (MCA), the Methamphetamine Anti-Proliferation Act of 2000 (MAPA), and the Combat Methamphetamine Epidemic Act of 2005 (CMEA). This is illustrated by changes in the patterns of diversion:

- » When the quantity of U.S. chemicals shipped to cocaine manufacturing areas declined, chemical suppliers from other parts of the world emerged as new sources of supply. The U.S. government then undertook an aggressive international campaign to educate and elicit the support of other nations in establishing chemical controls. Today, there is a broad level of international agreement regarding the actions that must be taken to achieve chemical control. Many nations have passed laws to prevent the diversion of chemicals.
- » As a result of government controls, ephedrine and other chemicals used to manufacture methamphetamine became more difficult to divert. Traffickers then began using over-the-counter capsules and tablets that contained these ingredients. As chemicals rendered into legitimate medicines purportedly for the commercial market, these products were exempted from the CDTA requirements. The DCDCA closed this loophole and required DEA registration for all manufacturers, distributors, importers, and exporters of List I chemicals. It also established recordkeeping and reporting requirements for transactions in single-entity ephedrine products.
- » When single-entity ephedrine products became regulated, drug traffickers turned to pseudoephedrine. This was

addressed by the MCA which expanded regulatory control of lawfully marketed drug products containing ephedrine, pseudoephedrine, and phenylpropanolamine (PPA)*.

- » MAPA focused on the continuing retail level diversion by constricting retail transactions of pseudoephedrine and PPA drug products. It reduced the threshold for such transactions from 24 grams to nine grams of pseudoephedrine or PPA base in a single transaction and limited package sizes to contain no more than three grams of pseudoephedrine or PPA base. The Act also increased penalties for chemical diversion and provided for restitution to the government for cleanup costs.
- » The CMEA further restricted retail level transactions by redefining nonprescription products that contain ephedrine, pseudoephedrine, and PPA as "scheduled listed chemical products (SLCPs)." The Act requires all regulated sellers of SLCPs to complete a required training and self-certification process effective September 30, 2006. On this date, stores were required to keep all SLCPs behind the counter or in a locked cabinet. Consumers wishing to purchase SLCPs are required to show identification and sign a logbook for each purchase. The Act also implements daily sales limits of 3.6 grams per purchaser and purchase limits of nine grams of these products in a 30 day period to any person.

All of these Federal laws (CDTA, DCDCA, MCA, MAPA, and CMEA) imposed varying degrees of reporting requirements on the chemical and pharmaceutical industries. Yet the involvement of private industry and the public should not be limited to the laws enacted by Congress. The voluntary support by industry constitutes a powerful resource for protecting the health and safety of the nation. DEA encourages each firm to be vigilant and to become a partner in combating the diversion of chemicals used in illegal drug production.

It is DEA's goal to effectively regulate while maintaining a positive working relationship with the regulated community

and seeks to educate the regulated community on the various laws regarding precursor chemicals and their implementing regulations. DEA understands that it can best serve the public interest by working in voluntary cooperation with the chemical industry in developing programs designed to prevent the diversion of regulated chemicals into the illicit market.

* Due to concerns regarding harmful side effects that phenylpropanolamine (PPA) can have, on November 6, 2000 the Food and Drug Administration required a voluntary withdrawal of over the counter PPA products intended for human consumption.

Table 1: Controlled Substances Produced

Controlled Substance	Controlled Substance Produced										Total	Total
	Codeine	Morfin	LSD	MBA	MDE	MMA	Mescaline	Mephedrone	Mephedrone	Mephedrone		
1. N-Acetyl-anthranilic Acid ¹							▲				40	40
2. Anthranilic Acid ²							▲				30	30
3. Benzaldehyde	■									▲	4	4
4. Benzyl Cyanide										▲	1	1
5. Ephedrine						▲	▲				0	0
6. Ergonovine			▲								0.010	0.010
7. Ergotamine			▲								0.020	0.020
8. Ethylamine ¹		▲			▲						1	1
9. Gamma-Butyrolactone (GBL)			▲								0	0
10. Hydriodic Acid						■					1.7	1.7
11. Hypophosphorous Acid ¹	■					■					0	0
12. Iodine	■					■					0	0
13. Isosafrole				▲	▲	▲					4	4
14. Methylamine ¹							▲	▲			1	1
15. 3, 4-Methylenedioxyphenyl-2-Propanone				▲	▲	▲					4	4
16. N-Methylephedrine ³		▲									1	1
17. N-Methylpseudoephedrine ³		▲									1	1
18. N-phenethyl-4-Piperidone (NPP)			▲								0	0
19. Nitroethane				▲						▲	2.5	2.5
20. Norpseudoephedrine ³		▲							▲		2.5	2.5
21. Phenylacetic Acid ⁴										▲	1	1
22. Phenylpropanolamine ^{1,3,7}		▲								▲	2.5	2.5
23. Phosphorus (red)	■					■					0	0
24. Phosphorus (white or yellow)	■					■					0	0
25. Piperidine ¹										▲	0.500	0.500
26. Piperonal				▲	▲	▲					4	4
27. Propionic Anhydride											0.001	0.001
28. Pseudoephedrine ^{1,3,7}							▲	▲			1	1
29. Safrole				▲	▲	▲					4	4



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IV Introduction to Drug Classes

The Controlled Substances Act (CSA) regulates five classes of drugs:

- Narcotics
- Depressants
- Stimulants
- Hallucinogens
- Anabolic steroids

Each class has distinguishing properties, and drugs within each class often produce similar effects. However, all controlled substances, regardless of class, share a number of common features. This introduction will familiarize you with these shared features and define the terms frequently associated with these drugs.

All controlled substances have abuse potential or are immediate precursors to substances with abuse potential. With the exception of anabolic steroids, controlled substances are abused to alter mood, thought, and feeling through their actions on the central nervous system (brain and spinal cord). Some of these drugs alleviate pain, anxiety, or depression. Some induce sleep and others energize.

Though some controlled substances are therapeutically useful, the "feel good" effects of these drugs contribute to their abuse. The extent to which a substance is reliably capable of producing intensely pleasurable feelings (euphoria) increases the likelihood of that substance being abused.

DRUG ABUSE

When drugs are used in a manner or amount inconsistent with the medical or social patterns of a culture, it is called drug abuse. The non-sanctioned use of substances controlled in Schedules I through V of the CSA is considered drug abuse. While legal pharmaceuticals placed under control in the CSA are prescribed and used by patients for medical treatment,

the use of these same pharmaceuticals outside the scope of sound medical practice is drug abuse.

DEPENDENCE

In addition to having abuse potential, most controlled substances are capable of producing dependence, either physical or psychological.

Physical Dependence

Physical dependence refers to the changes that have occurred in the body after repeated use of a drug that necessitates the continued administration of the drug to prevent a withdrawal syndrome. This withdrawal syndrome can range from mildly unpleasant to life-threatening and is dependent on a number of factors, such as:

- The drug being used
- The dose and route of administration
- Concurrent use of other drugs
- Frequency and duration of drug use
- The age, sex, health, and genetic makeup of the user

Psychological Dependence

Psychological dependence refers to the perceived "need" or "craving" for a drug. Individuals who are psychologically dependent on a particular substance often feel that they cannot function without continued use of that substance. While physical dependence disappears within days or weeks after drug use stops, psychological dependence can last much longer and is one of the primary reasons for relapse (initiation of drug use after a period of abstinence).

Contrary to common belief, physical dependence is not addiction. While addicts are usually physically dependent on the drug they are abusing, physical dependence can exist without addiction. For example, patients who take narcotics for chronic

pain management or benzodiazepines to treat anxiety are likely to be physically dependent on that medication.

ADDICTION

Addiction is defined as compulsive drug-seeking behavior where acquiring and using a drug becomes the most important activity in the user's life. This definition implies a loss of control regarding drug use, and the addict will continue to use a drug despite serious medical and/or social consequences. In 2009, an estimated 21.8 million Americans aged 12 or older were current (past month) illicit drug users, meaning they had used an illicit drug during the month prior to the survey interview. This estimate represents 8.7 percent of the population aged 12 or older. Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.¹

Drugs within a class are often compared with each other with terms like potency and efficacy. Potency refers to the amount of a drug that must be taken to produce a certain effect, while efficacy refers to whether or not a drug is capable of producing a given effect regardless of dose. Both the strength and the ability of a substance to produce certain effects play a role in whether that drug is selected by the drug abuser.

It is important to keep in mind that the effects produced by any drug can vary significantly and is largely dependent on the dose and route of administration. Concurrent use of other drugs can enhance or block an effect, and substance abusers often take more than one drug to boost the desired effects or counter unwanted side effects. The risks associated with drug abuse cannot be accurately predicted because each user has his/her own unique sensitivity to a drug. There are a number of theories that attempt to explain these differences, and it is clear that a genetic component may predispose an individual to certain toxicities or even addictive behavior.

Youth are especially vulnerable to drug abuse. According to NIDA, young Americans engaged in extraordinary levels of illicit drug use in the last third of the twentieth century. Today, about 47% of young people have used an illicit drug by the time they leave high school and about 16 percent of eighth, tenth, and

twelfth graders are current (within the past month) users.²

The behaviors associated with teen and preteen drug use often result in tragic consequences with untold harm to others, themselves, and their families. For example, an analysis of data from the National Survey on Drug Use and Health indicates that youth between the ages of 12 and 17 who had engaged in fighting or other delinquent behaviors were more likely than other youths to have used illicit drugs in the past month. For example, in 2009, past-month illicit drug use was reported by 18.8 percent of youths who had gotten into a serious fight at school or work in the past year, compared with 7.7 percent of those who had not engaged in fighting, and by 38.3 percent of those who had stolen or tried to steal something worth over \$50 in the past year compared with 8.7 percent of those who had not attempted or engaged in such theft.³

In the sections that follow, each of the five classes of drugs is reviewed and various drugs within each class are profiled. Although marijuana is classified in the CSA as a hallucinogen, a separate section is dedicated to that topic. There are also a number of substances that are abused but not regulated under the CSA. Alcohol and tobacco, for example, are specifically exempt from control by the CSA. In addition, a whole group of substances called inhalants are commonly available and widely abused by children. Control of these substances under the CSA would not only impede legitimate commerce, but also would likely have little effect on the abuse of these substances by youngsters. An energetic campaign aimed at educating both adults and youth about inhalants is more likely to prevent their abuse. To that end, a section is dedicated to providing information on inhalants.

¹ Results from *The 2009 National Survey on Drug Use and Health: Volume 1: Summary of National Findings*, U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration.

² *Monitoring the Future Survey, 2009*, National Institute on Drug Abuse, National Institutes of Health, U.S. Department of Health and Human Services.

³ *National Survey on Drug Use and Health, 2009*, U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration.



WHAT ARE NARCOTICS?

Also known as "opioids," the term "narcotic" comes from the Greek word for "stupor" and originally referred to a variety of substances that dulled the senses and relieved pain. Though some people still refer to all drugs as "narcotics," today "narcotic" refers to opium, opium derivatives, and their semi-synthetic substitutes. A more current term for these drugs, with less uncertainty regarding its meaning, is "opioid." Examples include the illicit drug heroin and pharmaceutical drugs like OxyContin®, Vicodin®, codeine, morphine, methadone, and fentanyl.

WHAT IS THEIR ORIGIN?

The poppy papaver somniferum is the source for all natural opioids, whereas synthetic opioids are made entirely in a lab and include meperidine, fentanyl, and methadone. Semi-synthetic opioids are synthesized from naturally occurring opium products, such as morphine and codeine, and include heroin, oxycodone, hydrocodone, and hydromorphone. Teens can obtain narcotics from friends, family members, medicine cabinets, pharmacies, nursing homes, hospitals, hospices, doctors, and the Internet.



What are common street names?

Street names for various narcotics/opioids include:

- Smack, Horse, Mud, Brown Sugar, Junk, Black Tat, Big H, Paregoric, Dover's Powder, MPTP (New Heroin), Hillbilly Heroin, Lean or Purple Drank, OC, Ox, Oxy, Oxycotton, Sippin Syrup

What do they look like?

Narcotics/opioids come in various forms, including:

- Tablets, capsules, skin patches, powder, chunks in varying colors (from white to shades of brown and black), liquid form for oral use and injection, syrups, suppositories, and lollipops

How are they abused?

- Narcotics/opioids can be swallowed, smoked, sniffed, or injected.

What is their effect on the mind?

Besides their medical use, narcotics/opioids produce a general sense of well-being by reducing tension, anxiety, and aggression. These effects are helpful in a therapeutic setting but contribute to the drugs' abuse. Narcotic/opioid use comes with a variety of unwanted effects, including drowsiness, inability to concentrate, and apathy.

Psychological dependence

Use can create psychological dependence. Long after the physical need for the drug has passed, the addict may continue to think and talk about using drugs and feel overwhelmed coping with daily activities. Relapse is common if there are not changes to the physical environment or the behavioral motivators that prompted the abuse in the first place.

What is their effect on the body?

Narcotics/opioids are prescribed by doctors to treat pain, suppress cough, cure diarrhea, and put people to sleep. Effects depend heavily on the dose, how it's taken, and previous exposure to the drug. Negative effects include:

→ Slowed physical activity, constriction of the pupils, flushing of the face and neck, constipation, nausea, vomiting, and slowed breathing

As the dose is increased, both the pain relief and the harmful effects become more pronounced. Some of these preparations are so potent that a single dose can be lethal to an inexperienced user. However, except in cases of extreme intoxication, there is no loss of motor coordination or slurred speech.

Physical dependence and withdrawal

Physical dependence is a consequence of chronic opioid use, and withdrawal takes place when drug use is discontinued. The intensity and character of the physical symptoms experienced during withdrawal are directly related to the particular drug used, the total daily dose, the interval between doses, the duration of use and the health and personality of the user. These symptoms usually appear shortly before the time of the next scheduled dose.

Early withdrawal symptoms often include:

→ Watery eyes, runny nose, yawning, and sweating

As the withdrawal worsens, symptoms can include:

→ Restlessness, irritability, loss of appetite, nausea, tremors, drug craving, severe depression, vomiting, increased heart rate and blood pressure, and chills alternating with flushing and excessive sweating

However, without intervention, the withdrawal usually runs its course, and most physical symptoms disappear within days or weeks, depending on the particular drug.

What are their overdose effects?

Overdoses of narcotics are not uncommon and can be fatal.

Physical signs of narcotics/opioid overdose include:

→ Constricted (pinpoint) pupils, cold clammy skin, confusion, convulsions, extreme drowsiness, and slowed breathing

Which drugs cause similar effects?

With the exception of pain relief and cough suppression, most central nervous system depressants (like barbiturates, benzodiazepines, and alcohol) have similar effects, including slowed breathing, tolerance, and dependence.

What is their legal status in the United States?

Narcotics/opioids are controlled substances that vary from Schedule I to Schedule V, depending on their medical usefulness, abuse potential, safety, and drug dependence profile. Schedule I narcotics, like heroin, have no medical use in the U.S. and are illegal to distribute, purchase, or use outside of medical research.

Heroin

WHAT IS HEROIN?

Heroin is a highly addictive drug and the most rapidly acting of the opiates.

WHAT IS ITS ORIGIN?

Heroin is processed from morphine, a naturally occurring substance extracted from the seed pod of certain varieties of poppy plants grown in:

- Southeast Asia (Thailand, Laos, and Myanmar (Burma)), Southwest Asia (Afghanistan and Pakistan), Mexico, and Colombia

It comes in several forms, the main one being "black tar" from Mexico (found primarily in the western United States) and white heroin from Colombia (primarily sold on the East Coast).

What are common street names?

Common street names for heroin include:

- Big H, Black Tar, Chiva, Hell Dust, Horse, Negra, Smack, and Thunder

What does it look like?

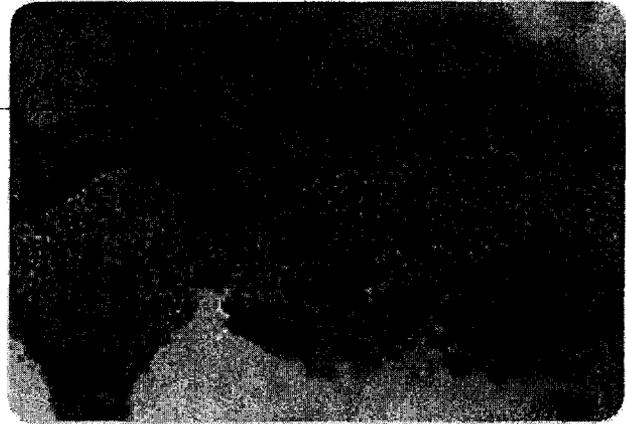
Heroin is typically sold as a white or brownish powder, or as the black sticky substance known on the streets as "black tar heroin." Although purer heroin is becoming more common, most street heroin is "cut" with other drugs or with substances such as sugar, starch, powdered milk, or quinine.

How is it abused?

Heroin can be injected, smoked, or sniffed/snorted. High purity heroin is usually snorted or smoked.

What is its effect on the mind?

Because it enters the brain so rapidly, heroin is particularly addictive, both psychologically and physically. Heroin abusers report feeling a surge of euphoria or "rush," followed by a twilight state of sleep and wakefulness.



Heroin

What is its effect on the body?

One of the most significant effects of heroin use is addiction. With regular heroin use, tolerance to the drug develops. Once this happens, the abuser must use more heroin to achieve the same intensity. As higher doses of the drug are used over time, physical dependence and addiction to the drug develop.

Physical symptoms of heroin use include:

- Drowsiness, respiratory depression, constricted pupils, nausea, a warm flushing of the skin, dry mouth, and heavy extremities

What are its overdose effects?

Because heroin abusers do not know the actual strength of the drug or its true contents, they are at a high risk of overdose or death.

The effects of a heroin overdose are:

- Slow and shallow breathing, blue lips and fingernails, clammy skin, convulsions, coma, and possible death

Which drugs cause similar effects?

Other opioids such as OxyContin®, Vicodin®, codeine, morphine, methadone, and fentanyl can cause similar effects as heroin.

What is its legal status in the United States?

Heroin is a Schedule I substance under the Controlled Substances Act meaning that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.

Hydromorphone

WHAT IS HYDROMORPHONE?

Hydromorphone belongs to a class of drugs called "opioids," which includes morphine. It has an analgesic potency of two to eight times that of morphine, but has a shorter duration of action and greater sedative properties.

WHAT IS ITS ORIGIN?

Hydromorphone is legally manufactured and distributed in the United States. However, abusers can obtain hydromorphone from forged prescriptions, "doctor-shopping," theft from pharmacies, and from friends and acquaintances.

What are the street names?

Common street names include:

→ D, Dillies, Dust, Footballs, Juice, and Smack

What does it look like?

Hydromorphone comes in:

→ Tablets, rectal suppositories, oral solutions, and injectable formulations

How is it abused?

Users may abuse hydromorphone tablets by ingesting them. Injectable solutions, as well as tablets that have been crushed and dissolved in a solution may be injected as a substitute for heroin.

What is its effect on the mind?

When used as a drug of abuse, and not under a doctor's supervision, hydromorphone is taken to produce feelings of euphoria, relaxation, sedation, and reduced anxiety. It may also cause mental clouding, changes in mood, nervousness, and restlessness. It works centrally (in the brain) to reduce pain and suppress cough. Hydromorphone use is associated with both physiological and psychological dependence.

What is its effect on the body?

Hydromorphone may cause:

→ Constipation, pupillary constriction, urinary retention, nausea, vomiting, respiratory depression, dizziness, impaired coordination, loss of appetite, rash, slow or rapid heartbeat, and changes in blood pressure

What are its overdose effects?

Acute overdose of hydromorphone can produce:

→ Severe respiratory depression, drowsiness progressing to stupor or coma, lack of skeletal muscle tone, cold and clammy skin, constricted pupils, and reduction in blood pressure and heart rate

Severe overdose may result in death due to respiratory depression.

Which drugs cause similar effects?

Drugs that have similar effects include:

→ Heroin, morphine, hydrocodone, fentanyl, and oxycodone

What is its legal status in the United States?

Hydromorphone is a Schedule II drug under the Controlled Substances Act with an accepted medical use as a pain reliever. Hydromorphone has a high potential for abuse and use may lead to severe psychological or physical dependence.

17 Narcotics

Methadone

WHAT IS METHADONE?

Methadone is a synthetic (man-made) narcotic.

WHAT IS ITS ORIGIN?

German scientists synthesized methadone during World War II because of a shortage of morphine. Methadone was introduced into the United States in 1947 as an analgesic (Dolophinel).

What are common street names?

Common street names include:

→ Amidone, Chocolate Chip Cookies, Fizzies, Maria, Pastora, Salvia, Street Methadone, and Wafer

What does it look like?

Methadone is available as a tablet, disc, oral solution, or injectable liquid. Tablets are available in 5 mg and 10 mg formulations. As of January 1, 2008, manufacturers of methadone hydrochloride tablets 40 mg (dispersible) have voluntarily agreed to restrict distribution of this formulation to only those facilities authorized for detoxification and maintenance treatment of opioid addiction, and hospitals. Manufacturers will instruct their wholesale distributors to discontinue supplying this formulation to any facility not meeting the above criteria.

How is it abused?

Methadone can be swallowed or injected.

What is its effect on the mind?

Abuse of methadone can lead to psychological dependence.

What is its effect on the body?

When an individual uses methadone, he/she may experience physical symptoms like sweating, itchy skin, or sleepiness. Individuals who abuse methadone risk becoming tolerant of and physically dependent on the drug.

When use is stopped, individuals may experience withdrawal symptoms including:

→ Anxiety, muscle tremors, nausea, diarrhea, vomiting, and abdominal cramps

What are its overdose effects?

The effects of a methadone overdose are:

→ Slow and shallow breathing, blue fingernails and lips, stomach spasms, clammy skin, convulsions, weak pulse, coma, and possible death

Which drugs cause similar effects?

Although chemically unlike morphine or heroin, methadone produces many of the same effects.

What is its legal status in the United States?

Methadone is a Schedule II drug under the Controlled Substances Act. While it may legally be used under a doctor's supervision, its non-medical use is illegal.



17-0001

Morphine

WHAT IS MORPHINE?

Morphine is a non-synthetic narcotic with a high potential for abuse and is the principal constituent of opium. It is one of the most effective drugs known for the relief of severe pain.

WHAT IS ITS ORIGIN?

In the United States, a small percentage of the morphine obtained from opium is used directly for pharmaceutical products. The remaining morphine is processed into codeine and other derivatives.

What are common street names?

Common street names include:

→ Dreamer, Emsel, First Line, God's Drug, Hows, M.S., Mister Blue, Morf, Morpho, and Unkie

What does it look like?

Morphine is marketed under generic and brand name products, including:

→ MS-Contin®, Oramorph SR®, MSIR®, Roxanol®, Kadian®, and RMS®

How is it abused?

Traditionally, morphine was almost exclusively used by injection, but the variety of pharmaceutical forms that it is marketed as today support its use by oral and other routes of administration.

Forms include:

→ Oral solutions, immediate-and sustained-release tablets and capsules, suppositories, and injectable preparations

Those dependent on morphine prefer injection because the drug enters the blood stream more quickly.

What is its effect on the mind?

Morphine's effects include euphoria and relief of pain. Chronic use of morphine results in tolerance and physical and psychological dependence.

What is its effect on the body?

Morphine use results in relief from physical pain, decrease in hunger, and inhibition of the cough reflex.

What are its overdose effects?

Overdose effects include:

→ Cold, clammy skin, lowered blood pressure, sleepiness, slowed breathing, slow pulse rate, coma, and possible death

Which drugs cause similar effects?

Drugs causing similar effects as morphine include:

→ Opium, codeine, heroin, methadone, hydrocodone, fentanyl, and oxycodone

What is its legal status in the United States?

Morphine is a Schedule II narcotic under the Controlled Substances Act.



Poppy plants are the source of opium, the natural source of morphine.

Opium

WHAT IS OPIUM?

Opium is a highly addictive non-synthetic narcotic that is extracted from the poppy plant, *Papaver somniferum*. The opium poppy is the key source for many narcotics, including morphine, codeine, and heroin.

WHAT IS ITS ORIGIN?

The poppy plant, *Papaver somniferum*, is the source of opium. It was grown in the Mediterranean region as early as 5,000 B.C., and has since been cultivated in a number of countries throughout the world. The milky fluid that seeps from its incisions in the unripe seed pod of this poppy has been scraped by hand and air-dried to produce what is known as opium.

A more modern method of harvesting for pharmaceutical use is by the industrial poppy straw process of extracting alkaloids from the mature dried plant (concentrate of poppy straw). All opium and poppy straw used for pharmaceutical products are imported into the United States from legitimate sources in regulated countries.

What are common street names?

Common street names include:

→ Ah-pen-yen, Aunti, Aunti Emma, Big O, Black Pill, Chandoo, Chandu, Chinese Molasses, Chinese Tobacco, Dopium, Dover's Powder, Dream Gun, Dream Stick, Dreams, Easing Powder, Fi-do-nie, Gee, God's Medicine, Gondola, Goric, Great Tobacco, Guma, Hop/hops, Joy Plant, Midnight Oil, Mira, O, O.P., Ope, Pen Yan, Pin Gon, Pox, Skee, Toxy, Toys, When-shee, Ze, and Zero

What does it look like?

Opium can be a liquid, solid, or powder, but most poppy straw concentrate is available commercially as a fine brownish powder.

How is it abused?

Opium can be smoked, intravenously injected, or taken in pill form. Opium is also abused in combination with other drugs. For example, "Black" is a combination of marijuana, opium, and methamphetamine, and "Buddha" is potent marijuana spiked with opium.

What is its effect on the mind?

The intensity of opium's euphoric effects on the brain depends on the dose and route of administration. It works quickly when smoked because the opiate chemicals pass into the lungs, where they are quickly absorbed and then sent to the brain. An opium "high" is very similar to a heroin "high"; users experience a euphoric rush, followed by relaxation and the relief of physical pain.

What is its effect on the body?

Opium inhibits muscle movement in the bowels leading to constipation. It also can dry out the mouth and mucous membranes in the nose. Opium use leads to physical and psychological dependence, and can lead to overdose.

What are its overdose effects?

Overdose effects include:

→ Slow breathing, seizures, dizziness, weakness, loss of consciousness, coma, and possible death

Which drugs cause similar effects?

Drugs that cause similar effects include:

→ Morphine, codeine, heroin, methadone, hydroquinone, fentanyl, and oxycodone

What is its legal status in the United States?

Opium is a Schedule II drug under the Controlled Substances Act. Most opioids are Schedule II, III, IV, or V drugs. Some drugs that are derived from opium, such as heroin, are Schedule I drugs.

Oxycodone

WHAT IS OXYCODONE?

Oxycodone is a semi-synthetic narcotic analgesic and historically has been a popular drug of abuse among the narcotic abusing population.

WHAT IS ITS ORIGIN?

Oxycodone is synthesized from thebaine, a constituent of the poppy plant.

What are common street names?

Common street names for Oxycodone include:

→ Hillbilly Heroin, Kicker, OC, Ox, Roxy, Perc, and Oxy

What does it look like?

Oxycodone is marketed alone as OxyContin® in 10, 20, 40 and 80 mg controlled-release tablets and other immediate-release capsules like 5 mg OxyIR®. It is also marketed in combination products with aspirin such as Percodan® or acetaminophen such as Roxicet®.

How is it abused?

Oxycodone is abused orally or intravenously. The tablets are crushed and sniffed or dissolved in water and injected. Others heat a tablet that has been placed on a piece of foil then inhale the vapors.

What is its effect on the mind?

Euphoria and feelings of relaxation are the most common effects of oxycodone on the brain, which explains its high potential for abuse.

What is its effect on the body?

Physiological effects of oxycodone include:

→ Pain relief, sedation, respiratory depression, constipation, papillary constriction, and cough suppression. Extended or chronic use of oxycodone containing acetaminophen may cause severe liver damage.

What are its overdose effects?

Overdose effects include:

→ Extreme drowsiness, muscle weakness, confusion, cold and clammy skin, pinpoint pupils, shallow breathing, slow heart rate, fainting, coma, and possible death

Which drugs cause similar effects?

Drugs that cause similar effects to Oxycodone include:

→ Opium, codeine, heroin, methadone, hydrocodone, fentanyl, and morphine

What is its legal status in the United States?

Oxycodone products are in Schedule II of the federal Controlled Substances Act of 1970.



VI. Stimulants

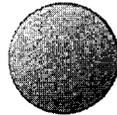
WHAT ARE STIMULANTS?

Stimulants speed up the body's systems. This class of drugs includes:

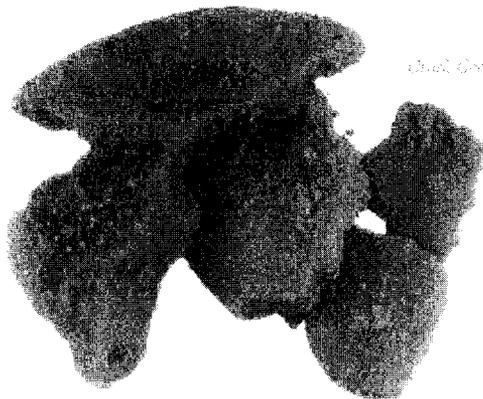
→ Prescription drugs such as amphetamines [Adderall® and Dexedrine®], methylphenidate [Concerta® and Ritalin®], diet aids [such as Didrex®, Bontril®, Preludin®, Fastin®, Adipex P®, Ionomin®, and Meridia®] and illicitly produced drugs such as methamphetamine, cocaine, and methcathinone.

WHAT IS THEIR ORIGIN?

Stimulants are diverted from legitimate channels and clandestinely manufactured exclusively for the illicit market.



Ritalin® SR 20mg tablet



Crack Cocaine

What are common street names?

Common street names include:

→ Bennies, Black Beauties, Cat, Coke, Crank, Crystal, Flake, Ice, Pellets, R-Ball, Skippy, Snow, Speed, Uppers, and Vitamin R

What do they look like?

Stimulants come in the form of:

→ Pills, powder, rocks, and injectable liquids

How are they abused?

Stimulants can be pills or capsules that are swallowed. Smoking, snorting, or injecting stimulants produces a sudden sensation known as a "rush" or a "flash."

Abuse is often associated with a pattern of binge use — sporadically consuming large doses of stimulants over a short period of time. Heavy users may inject themselves

every few hours, continuing until they have depleted their drug supply or reached a point of delirium, psychosis, and physical exhaustion. During heavy use, all other interests become secondary to recreating the initial euphoric rush.

What is their effect on the mind?

When used as drugs of abuse and not under a doctor's supervision, stimulants are frequently taken to:

- Produce a sense of exhilaration, enhance self esteem, improve mental and physical performance, increase activity, reduce appetite, extend wakefulness for prolonged period, and "get high"

Chronic, high-dose use is frequently associated with agitation, hostility, panic, aggression, and suicidal or homicidal tendencies.

Paranoia, sometimes accompanied by both auditory and visual hallucinations, may also occur.

Tolerance, in which more and more drug is needed to produce the usual effects, can develop rapidly, and psychological dependence occurs. In fact, the strongest psychological dependence observed occurs with the more potent stimulants, such as amphetamine, methylphenidate, methamphetamine, cocaine and methcathinone.

Abrupt cessation is commonly followed by depression, anxiety, drug craving, and extreme fatigue, known as a "crash."

What is their effect on the body?

Stimulants are sometimes referred to as uppers and reverse the effects of fatigue on both mental and physical tasks. Therapeutic levels of stimulants can produce exhilaration, extended wakefulness, and loss of appetite. These effects are greatly intensified when large doses of stimulants are taken.

Taking too large a dose at one time or taking large doses over an extended period of time may cause such physical side effects as:

- Dizziness, tremors, headache, flushed skin, chest pain with palpitations, excessive sweating, vomiting, and abdominal cramps

What are their overdose effects?

In overdose, unless there is medical intervention, high fever, convulsions, and cardiovascular collapse may precede death. Because accidental death is partially due to the effects of stimulants on the body's cardiovascular and temperature-regulating systems, physical exertion increases the hazards of stimulant use.

Which drugs cause similar effects?

Some hallucinogenic substances, such as Ecstasy, have a stimulant component to their activity.

What is their legal status in the United States?

Many stimulants have a legitimate medical use for the treatment of conditions such as obesity, narcolepsy, and attention deficit and hyperactivity disorder. Such stimulants vary in their level of control from Schedules II to IV, depending on their potential for abuse and dependence.

A number of stimulants have no medical use in the United States but have a high potential for abuse. These stimulants are controlled in Schedule I. Some prescription stimulants are not controlled, and some stimulants like tobacco and caffeine don't require a prescription — though society's recognition of their adverse effects has resulted in a proliferation of caffeine-free products and efforts to discourage cigarette smoking.

Stimulant chemicals in over-the-counter products, such as ephedrine and pseudoephedrine can be found in allergy and cold medicine. As required by The Combat Methamphetamine Epidemic Act of 2005, a retail outlet must store these products out of reach of customers, either behind the counter or in a locked cabinet. Regulated sellers are required to maintain a written or electronic form of a logbook to record sales of these products. In order to purchase these products, customers must now show a photo identification issued by a state or federal government. They are also required to write or enter into the logbook: their name, signature, address, date, and time of sale. In addition to the above, there are daily and monthly sales limits set for customers.

VI. Stimulants

Amphetamines

WHAT ARE AMPHETAMINES?

Amphetamines are stimulants that speed up the body's system. Many are legally prescribed and used to treat attention-deficit hyperactivity disorder (ADHD).

WHAT IS THEIR ORIGIN?

Amphetamine was first marketed in the 1930s as Benzedrine® in an over-the-counter inhaler to treat nasal congestion. By 1937 amphetamine was available by prescription in tablet form and was used in the treatment of the sleeping disorder, narcolepsy, and ADHD.

Over the years, the use and abuse of clandestinely produced amphetamines have spread. Today, clandestine laboratory production of amphetamines has mushroomed, and the abuse of the drug has increased dramatically.

What are common street names?

Common street names include:

→ Bennies, Black Beauties, Crank, Ice, Speed, and Uppers

What do they look like?

Amphetamines can look like pills or powder. Common prescription amphetamines include methylphenidate (Ritalin® or Ritalin SR®), amphetamine and dextroamphetamine (Adderall®), and dextroamphetamine (Dexedrine®).

How are they abused?

Amphetamines are generally taken orally or injected. However, the addition of "ice," the slang name of crystallized methamphetamine hydrochloride, has promoted smoking as another mode of administration. Just as "crack" is smokable cocaine, "ice" is smokable methamphetamine.

What is their effect on the mind?

The effects of amphetamines and methamphetamine are similar to cocaine, but their onset is slower and their duration is longer. In contrast to cocaine, which is quickly removed from the brain and is almost completely metabolized, methamphetamine

remains in the central nervous system longer, and a larger percentage of the drug remains unchanged in the body, producing prolonged stimulant effects.

Chronic abuse produces a psychosis that resembles schizophrenia and is characterized by: Paranoia, picking at the skin, preoccupation with one's own thoughts, and auditory and visual hallucinations. Violent and erratic behavior is frequently seen among chronic abusers of amphetamines and methamphetamine.

What is their effect on the body?

Physical effects of amphetamine use include:

→ Increased blood pressure and pulse rates, insomnia, loss of appetite, and physical exhaustion

What are their overdose effects?

Overdose effects include:

→ Agitation, increased body temperature, hallucinations, convulsions, and possible death

Which drugs cause similar effects?

Drugs that cause similar effects include:

→ Dexmethylphenidate, phentermine, benzphetamine, phendimetrazine, cocaine, crack, methamphetamine, and khat

What is their legal status in the United States?

Amphetamines are Schedule II stimulants, which means that they have a high potential for abuse and limited medical uses. Pharmaceutical products are available only through a prescription that cannot be refilled.

Cocaine

WHAT IS COCAINE?

Cocaine is an intense, euphoria-producing stimulant drug with strong addictive potential.

WHAT IS ITS ORIGIN?

Cocaine is derived from coca leaves grown in Bolivia, Peru, and Colombia. The cocaine manufacturing process takes place in remote jungle labs where the raw product undergoes a series of chemical transformations. Colombia produces about 90% of the cocaine powder reaching the United States. According to the 2005 Colombia Threat Assessment, 90% of the cocaine shipped to the United States comes from the Central America-Mexico corridor.

What are common street names?

Common street names include:

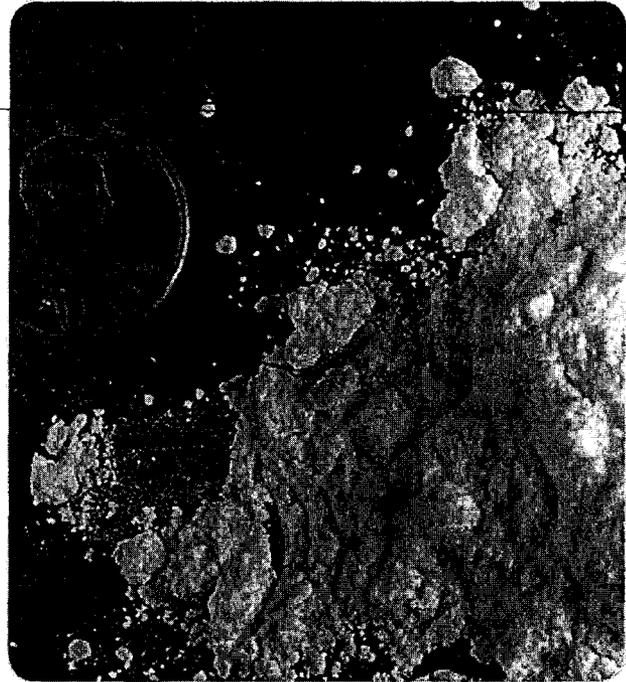
→ Coca, Coke, Crack, Flake, Snow, and Soda Cot

What does it look like?

Cocaine is usually distributed as a white, crystalline powder. Cocaine is often diluted ("cut") with a variety of substances, the most common of which are sugars and local anesthetics. It is "cut" to stretch the amount of the product and increase profits for dealers. In contrast, cocaine base (crack) looks like small, irregularly shaped chunks (or "rocks") of a whitish solid.

How is it abused?

Powdered cocaine can be snorted or injected into the veins after dissolving in water. Cocaine base (crack) is smoked, either alone or on marijuana or tobacco. Cocaine is also abused in combination with an opiate, like heroin, a practice known as "speedballing." Although injecting into veins or muscles, snorting, and smoking are the common ways of using cocaine, all mucous membranes readily absorb cocaine. Cocaine users typically binge on the drug until they are exhausted or run out of cocaine.



Cocaine powder

What is its effect on the mind?

The intensity of cocaine's euphoric effects depends on how quickly the drug reaches the brain, which depends on the dose and method of abuse. Following smoking or intravenous injection, cocaine reaches the brain in seconds, with a rapid buildup in levels. This results in a rapid-onset, intense euphoric effect known as a "rush."

By contrast, the euphoria caused by snorting cocaine is less intense and does not happen as quickly due to the slower build-up of the drug in the brain. Other effects include increased alertness and excitation, as well as restlessness, irritability, and anxiety.

Tolerance to cocaine's effects develops rapidly, causing users to take higher and higher doses. Taking high doses of cocaine or prolonged use, such as bingeing, usually causes paranoia. The crash that follows euphoria is characterized by mental and physical exhaustion, sleep, and depression lasting several days. Following the crash, users experience a craving to use cocaine again.

VI Stimulants

What is its effect on the body?

Physiological effects of cocaine include increased blood pressure and heart rate, dilated pupils, insomnia, and loss of appetite. The widespread abuse of highly pure street cocaine has led to many severe adverse health consequences such as:

→ Cardiac arrhythmias, ischemic heart conditions, sudden cardiac arrest, convulsions, strokes, and death

In some users, the long-term use of inhaled cocaine has led to a unique respiratory syndrome, and chronic snorting of cocaine has led to the erosion of the upper nasal cavity.

Which drugs cause similar effects?

Other stimulants, such as methamphetamine, cause effects similar to cocaine that vary mainly in degree.

What is its legal status in the United States?

Cocaine is a Schedule II drug under the Controlled Substances Act, meaning it has a high potential for abuse and limited medical usage. Cocaine hydrochloride solution (4% and 10%) is used primarily as a topical local anesthetic for the upper respiratory tract. It also is used to reduce bleeding of the mucous membranes in the mouth, throat, and nasal cavities. However, better products have been developed for these purposes, and cocaine is rarely used medically in the United States.



Figure 1. Cocaine (10)

Khat

WHAT IS KHAT?

Khat is a flowering evergreen shrub that is abused for its stimulant-like effect. Khat has two active ingredients, cathine and cathinone.

WHAT IS ITS ORIGIN?

Khat is native to East Africa and the Arabian Peninsula, where the use of it is an established cultural tradition for many social situations



© iStock.com

What are common street names?

Common street names for Khat include:

→ Abyssinian Tea, African Salad, Catha, Chat, Kat, and Oat

What does it look like?

Khat is a flowering evergreen shrub. Khat that is sold and abused is usually just the leaves, twigs, and shoots of the Khat shrub.

How is it abused?

Khat is typically chewed like tobacco, then retained in the cheek and chewed intermittently to release the active drug, which produces a stimulant-like effect. Dried Khat leaves can be made into tea or a chewable paste, and Khat can also be smoked and even sprinkled on food.

What is its effect on the mind?

Khat can induce manic behavior with:

→ Grandiose delusions, paranoia, nightmares, hallucinations, and hyperactivity

Chronic Khat abuse can result in violence and suicidal depression.

What is its effect on the body?

Khat causes an immediate increase in blood pressure and heart rate. Khat can also cause a brown staining of the teeth, insomnia, and gastric disorders. Chronic abuse of Khat can cause physical exhaustion.

What are its overdose effects?

The dose needed to constitute an overdose is not known, however it has historically been associated with those who have been long-term chewers of the leaves. Symptoms of toxicity include:

→ Delusions, loss of appetite, difficulty with breathing, and increases in both blood pressure and heart rate

Additionally, there are reports of liver damage (chemical hepatitis) and of cardiac complications, specifically myocardial infarctions. This mostly occurs among long-term chewers of khat or those who have chewed too large a dose.

Which drugs cause similar effects?

Khat's effects are similar to other stimulants, such as cocaine and methamphetamine.

What is its legal status in the United States?

The chemicals found in khat are controlled under the Controlled Substances Act. Cathine is a Schedule IV stimulant, and cathinone is a Schedule I stimulant under the Controlled Substances Act, meaning that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.

Methamphetamine

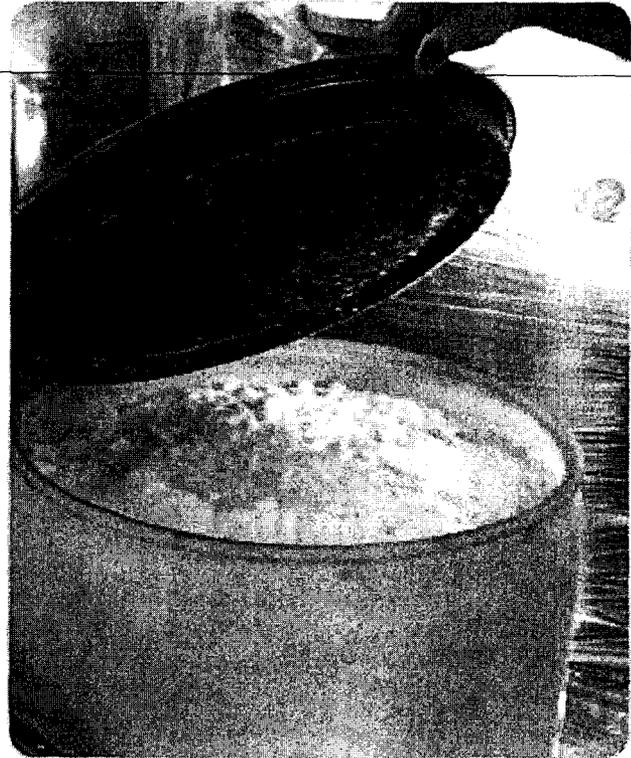
WHAT IS METHAMPHETAMINE?

Methamphetamine (meth) is a stimulant. The FDA-approved brand-name medication is Desoxyn®.

WHAT IS ITS ORIGIN?

Mexican drug trafficking organizations have become the primary manufacturers and distributors of methamphetamine to cities throughout the United States, including in Hawaii. Domestic clandestine laboratory operators also produce and distribute meth but usually on a smaller scale. The methods used depend on the availability of precursor chemicals.

Currently, meth is mainly made with diverted products that contain pseudoephedrine. The Combat Methamphetamine Epidemic Act of 2005 requires retailers of non-prescription products containing pseudoephedrine, ephedrine, or phenylpropanolamine to place these products behind the counter or in a locked cabinet. Consumers must show identification and sign a logbook for each purchase.



Methamphetamine, Crystal Meth

What are common street names?

Common street names include:

→ Batu, Bikers Coffee, Black Beauties, Chalk, Chicken Feed, Crank, Crystal, Glass, Go-Fast, Hiropon, Ice, Meth, Methlies Quick, Poor Man's Cocaine, Shabu, Shards, Speed, Stove Top, Tina, Trash, Tweak, Uppers, Ventana, Vidrio, Yaba, and Yellow Bam

What does it look like?

Regular meth is a pill or powder. Crystal meth resembles glass fragments or shiny blue-white "rocks" of various sizes.

How is it abused?

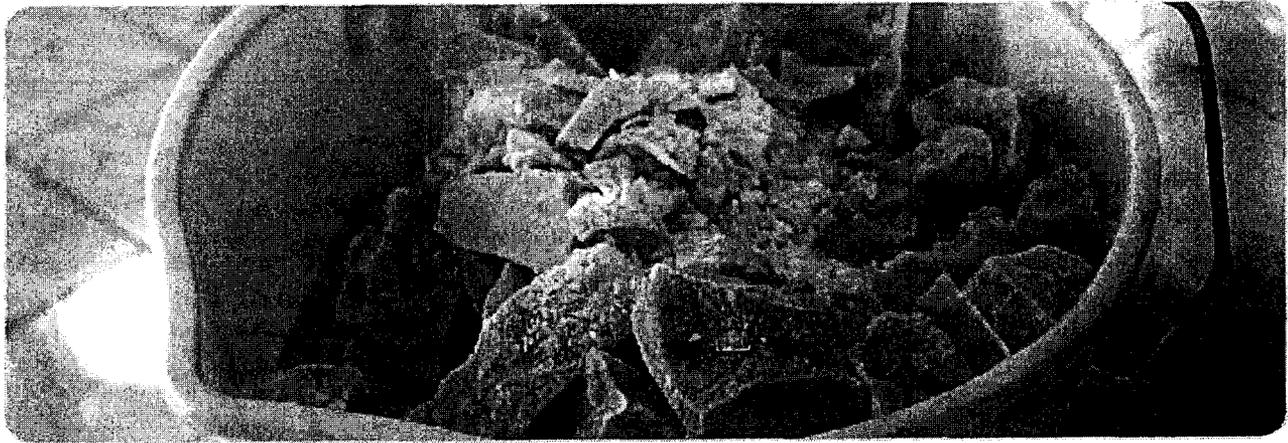
Meth is swallowed, snorted, injected, or smoked. To intensify the effects, users may take higher doses of the drug, take it more frequently, or change their method of intake.

In some cases, meth abusers go without food and sleep while taking part in a form of bingeing known as a "run." Meth users on a "run" inject as much as a gram of the drug every two to three hours over several days until they run out of meth or become too disorganized to continue.

What is its effect on the mind?

Meth is a highly addictive drug with potent central nervous system (CNS) stimulant properties.

Those who smoke or inject it report a brief, intense sensation, or rush. Oral ingestion or snorting produces a long-lasting high instead of a rush, which reportedly can continue for as long as half a day. Both the rush and the high are believed to result from the release of very high levels of the neurotransmitter dopamine into areas of the brain that regulate feelings of pleasure. Long-term meth use results in many damaging effects, including addiction.



All things) made in finished form

Chronic meth abusers exhibit violent behavior, anxiety, confusion, insomnia, and psychotic features including paranoia, aggression, visual and auditory hallucinations, mood disturbances, and delusions — such as the sensation of insects creeping on or under the skin.

Such paranoia can result in homicidal or suicidal thoughts. Researchers have reported that as much as 50% of the dopamine-producing cells in the brain can be damaged after prolonged exposure to relatively low levels of meth. Researchers also have found that serotonin-containing nerve cells may be damaged even more extensively.

What is its effect on the body?

Taking even small amounts of meth can result in:

- Increased wakefulness, increased physical activity, decreased appetite, rapid breathing and heart rate, irregular heartbeat, increased blood pressure, and hyperthermia (overheating)

High doses can elevate body temperature to dangerous, sometimes lethal, levels, and cause convulsions and even cardiovascular collapse and death. Meth abuse may also cause extreme anorexia, memory loss, and severe dental problems.

What are its overdose effects?

High doses may result in death from stroke, heart attack, or multiple organ problems caused by overheating.

Which drugs cause similar effects?

Cocaine and potent stimulant pharmaceuticals, such as amphetamines and methylphenidate, produce similar effects.

What is its legal status in the United States?

Methamphetamine is a Schedule II stimulant under the Controlled Substances Act, which means that it has a high potential for abuse and limited medical use. It is available only through a prescription that cannot be refilled. Today there is only one legal meth product, Desoxyn®. It is currently marketed in 5-milligram tablets and has very limited use in the treatment of obesity and attention deficit hyperactivity disorder (ADHD).



VII. Depressants

WHAT ARE DEPRESSANTS?

Depressants will put you to sleep, relieve anxiety and muscle spasms, and prevent seizures.

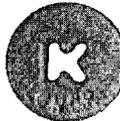
Barbiturates are older drugs and include butalbital (Fiorina®), phenobarbital, Pentothal®, Seconal® and Nembutal®. You can rapidly develop dependence on and tolerance to barbiturates, meaning you need more and more of them to feel and function normally. This makes them unsafe, increasing the likelihood of coma or death.

Benzodiazepines were developed to replace barbiturates, though they still share many of the undesirable side effects. Some examples are Valium®, Xanax®, Halcion®, Ativan®, Klonopin® and Restoril®. Rohypnol® is a benzodiazepine that is not manufactured or legally marketed in the United States, but it is used illegally.

Ambien® and Sonata® are sedative-hypnotic medications approved for the short-term treatment of insomnia that share many of the properties of benzodiazepines. Other CNS depressants include meprobamate, methaqualone (Quaalude®), and the illicit drug GHB.

WHAT IS THEIR ORIGIN?

Generally, legitimate pharmaceutical products are diverted to the illicit market. Teens can obtain depressants from the family medicine cabinet, friends, family members, the Internet, doctors, and hospitals.



Alprazolam 3.5 mg tablet



Phenobarbital 60 mg tablet

What are common street names?

Common street names for depressants include:

- Barbs, Benzos, Downers, Georgia Home Boy, GHB, Grievous Bodily Harm, Liquid X, Nerve Pills, Phennies, R2, Reds, Roofies, Rophies, Tranks, and Yellow

What do they look like?

Depressants come in the form of pills, syrups, and injectable liquids.

How are they abused?

Individuals abuse depressants to experience euphoria. Depressants are also used with other drugs to add to the other drugs' high or to deal with their side effects. Abusers take higher doses than people taking the drugs under a doctor's supervision for therapeutic purposes. Depressants like GHB and Rohypnol® are also misused to facilitate sexual assault.

What is their effect on the mind?

Depressants used therapeutically do what they are prescribed for:

- to put you to sleep, relieve anxiety and muscle spasms, and prevent seizures

They also:

- Cause amnesia, leaving no memory of events that occur while under the influence, reduce your reaction time, impair mental functioning and judgment, and cause confusion

Long-term use of depressants produces psychological dependence and tolerance.

What is their effect on the body?

Some depressants can relax the muscles. Unwanted physical effects include:

- Slurred speech, loss of motor coordination, weakness, headache, lightheadedness, blurred vision, dizziness, nausea, vomiting, low blood pressure, and slowed breathing

Prolonged use of depressants can lead to physical dependence even at doses recommended for medical treatment. Unlike barbiturates, large doses of benzodiazepines are rarely fatal unless combined with other drugs or alcohol. But unlike the withdrawal syndrome seen with most other drugs of abuse, withdrawal from depressants can be life threatening.

What are their overdose effects?

High doses of depressants or use of them with alcohol or other drugs can slow heart rate and breathing enough to cause death.

Which drugs cause similar effects?

Some antipsychotics, antihistamines, and antidepressants produce sedative effects. Alcohol's effects are similar to those of depressants.

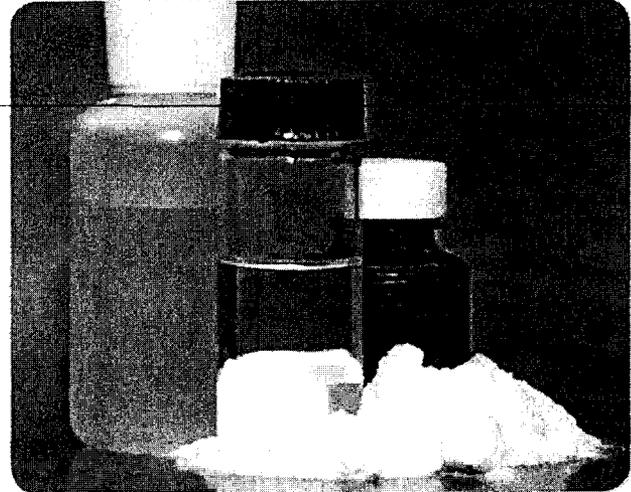


Photo courtesy of NIDA

What is their legal status in the United States?

Most depressants are controlled substances that range from Schedule I to Schedule IV under the Controlled Substances Act, depending on their risk for abuse and whether they currently have an accepted medical use. Many of the depressants have FDA-approved medical uses. Rohypnol® is not manufactured or legally marketed in the United States.

VII. Depressants

Barbiturates

WHAT ARE BARBITURATES?

Barbiturates are depressants that produce a wide spectrum of central nervous system depression from mild sedation to coma. They have also been used as sedatives, hypnotics, anesthetics, and anticonvulsants.

Barbiturates are classified as:

→ Ultrashort, Short, Intermediate, Long-acting

WHAT IS THEIR ORIGIN?

Barbiturates were first introduced for medical use in the 1900s, and today about 12 substances are in medical use.

What are common street names?

Common street names include:

→ Barbs, Block Busters, Christmas Trees, Goof Balls, Pinks, Red Devils, Reds & Blues, and Yellow Jackets

What do they look like?

Barbiturates come in a variety of multicolored pills and tablets. Abusers prefer the short-acting and intermediate barbiturates such as Amytal® and Seconal®.

How are they abused?

Barbiturates are abused by swallowing a pill or injecting a liquid form. Barbiturates are generally abused to reduce anxiety, decrease inhibitions, and treat unwanted effects of illicit drugs. Barbiturates can be extremely dangerous because overdoses can occur easily and lead to death.

What is their effect on the mind?

Barbiturates cause:

→ Mild euphoria, lack of inhibition, relief of anxiety, and sleepiness

Higher doses cause:

→ Impairment of memory, judgment, and coordination; irritability; and paranoid and suicidal ideation

Tolerance develops quickly and larger doses are then needed to produce the same effect, increasing the danger of an overdose.

What is their effect on the body?

Barbiturates slow down the central nervous system and cause sleepiness.

What are their overdose effects?

Effects of overdose include:

→ Shallow respiration, clammy skin, dilated pupils, weak and rapid pulse, coma, and possible death

Which drugs cause similar effects?

Drugs with similar effects include:

→ Alcohol, benzodiazepines like Valium® and Xanax®, tranquilizers, sleeping pills, Rohypnol®, and GHB

What is their legal status in the United States?

Barbiturates are Schedule II, III, and IV depressants under the Controlled Substances Act.

Benzodiazepines

WHAT ARE BENZODIAZEPINES?

Benzodiazepines are depressants that produce sedation, induce sleep, relieve anxiety and muscle spasms, and prevent seizures.

WHAT IS THEIR ORIGIN?

Benzodiazepines are only legally available through prescription. Many abusers maintain their drug supply by getting prescriptions from several doctors, forging prescriptions, or buying them illicitly. Alprazolam and diazepam are the two most frequently encountered benzodiazepines on the illicit market.

What are common street names?

Common street names include Benzos and Downers.

What do they look like?

The most common benzodiazepines are the prescription drugs Valium®, Xanax®, Halcion®, Ativan®, and Klonopin®. Tolerance can develop, although at variable rates and to different degrees. Shorter-acting benzodiazepines used to manage insomnia include estazolam (ProSom®), flurazepam (Dalmane®), temazepam (Restoril®), and triazolam (Halcion®). Midazolam (Versed®), a short-acting benzodiazepine, is utilized for sedation, anxiety, and amnesia in critical care settings and prior to anesthesia. It is available in the United States as an injectable preparation and as a syrup (primarily for pediatric patients).

Benzodiazepines with a longer duration of action are utilized to treat insomnia in patients with daytime anxiety. These benzodiazepines include alprazolam (Xanax®), chlordiazepoxide (Librium®), clorazepate (Tranxene®), diazepam (Valium®), halazepam (Paxipam®), lorazepam (Ativan®), oxazepam (Serax®), prazepam (Centrax®), and quazepam (Doral®). Clonazepam (Klonopin®), diazepam, and clorazepate are also used as anticonvulsants.

How are they abused?

Abuse is frequently associated with adolescents and young adults who take the drug orally or crush it up and snort it to get high. Abuse is particularly high among heroin and cocaine abusers.

What is their effect on the mind?

Benzodiazepines are associated with amnesia, hostility, irritability, and vivid or disturbing dreams.

What is their effect on the body?

Benzodiazepines slow down the central nervous system and may cause sleepiness.

What are their overdose effects?

Effects of overdose include:

→ Shallow respiration, clammy skin, dilated pupils, weak and rapid pulse, coma, and possible death

Which drugs cause similar effects?

Drugs that cause similar effects include:

→ Alcohol, barbiturates, sleeping pills, and GHB

What is their legal status in the United States?

Benzodiazepines are controlled in Schedule IV of the Controlled Substance Act.

VII. Depressants

GHB

WHAT IS GHB?

Gamma-Hydroxybutyric acid (GHB) is another name for the generic drug sodium oxybate. Xyrem® (which is sodium oxybate) is the trade name of the Food and Drug Administration (FDA)-approved prescription medication.

Analogues that are often substituted for GHB include GBL (gamma butyrolactone) and 1,4 BD (also called just "BD"), which is 1,4-butanediol. These analogues are available legally as industrial solvents used to produce polyurethane, pesticides, elastic fibers, pharmaceuticals, coatings on metal or plastic, and other products. They are also sold illicitly as supplements for bodybuilding, fat loss, reversal of baldness, improved eyesight, and to combat aging, depression, drug addiction, and insomnia.

GBL and BD are sold as "fish tank cleaner," "ink stain remover," "ink cartridge cleaner" and "nail enamel remover" for approximately \$100 per bottle — much more expensive than comparable products. Attempts to identify the abuse of GHB analogues are hampered by the fact that routine toxicological screens do not detect the presence of these analogues.

WHAT IS ITS ORIGIN?

GHB is produced illegally in both domestic and foreign clandestine laboratories. The major source of GHB on the street is through clandestine synthesis by local operators. At bars or "rave" parties, GHB is typically sold in liquid form by the capful or "swig" for \$5 to \$25 per cap. Xyrem® has the potential for diversion and abuse like any other pharmaceutical containing a controlled substance.

GHB has been encountered in nearly every region of the country.

What are common street names?

Common street names include:

- Easy Lay, G, Georgia Home Boy, GHB, Goop, Grievous Bodily Harm, Liquid Ecstasy, Liquid X, and Scoop

What does it look like?

GHB is usually sold as a liquid or as a white powder that is dissolved in a liquid, such as water, juice, or alcohol. GHB dissolved in liquid has been packaged in small vials or small water bottles. In liquid form, GHB is clear and colorless and slightly salty in taste.

How is it abused?

GHB and its analogues are abused for their euphoric and calming effects and because some people believe they build muscles and cause weight loss.

GHB and its analogues are also misused for their ability to increase libido, suggestibility, passivity, and to cause amnesia (no memory of events while under the influence of the substance) — traits that make users vulnerable to sexual assault and other criminal acts.

GHB abuse became popular among teens and young adults at dance clubs and "raves" in the 1990s and gained notoriety as a date rape drug. GHB is taken alone or in combination with other drugs, such as alcohol (primarily), other depressants, stimulants, hallucinogens, and marijuana.

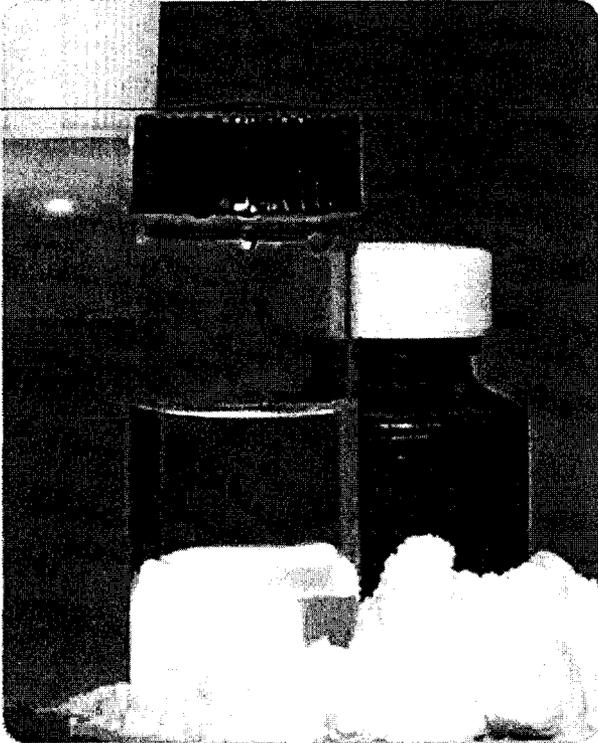
The average dose ranges from 1 to 5 grams (depending on the purity of the compound, this can be 1-2 teaspoons mixed in a beverage). However, the concentrations of these "home-brews" have varied so much that users are usually unaware of the actual dose they are drinking.

What is its effect on the mind?

GHB occurs naturally in the central nervous system in very small amounts. Use of GHB produces Central Nervous System (CNS) depressant effects including:

- Euphoria, drowsiness, decreased anxiety, confusion, and memory impairment

GHB can also produce both visual hallucinations and — paradoxically — excited and aggressive behavior. GHB greatly increases the CNS depressant effects of alcohol and other depressants.



White crystalline GHB

What is its effect on the body?

GHB takes effect in 15 to 30 minutes, and the effects last 3 to 6 hours. Low doses of GHB produce nausea.

At high doses, GHB overdose can result in:

- Unconsciousness, seizures, slowed heart rate, greatly slowed breathing, lower body temperature, vomiting, nausea, coma, and death

Regular use of GHB can lead to addiction and withdrawal that includes:

- Insomnia, anxiety, tremors, increased heart rate and blood pressure, and occasional psychotic thoughts

Currently, there is no antidote available for GHB intoxication.

GHB analogues are known to produce side effects such as:

- Topical irritation to the skin and eyes, nausea, vomiting, incontinence, loss of consciousness, seizures, liver damage, kidney failure, respiratory depression, and death

What are its overdose effects?

GHB overdose can cause death.

Which drugs cause similar effects?

GHB analogues are often abused in place of GHB. Both GBL and BD metabolize to GHB when taken and produce effects similar to GHB.

CNS depressants such as barbiturates and methaqualone also produce effects similar to GHB.

What is its legal status in the United States?

GHB is a Schedule I controlled substance, meaning that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. GHB products are Schedule III substances under the Controlled Substances Act. In addition, GBL is a List I chemical.

It was placed on Schedule I of the Controlled Substances Act in March 2000. However, when sold as GHB products (such as Xyrem®), it is considered Schedule III, one of several drugs that are listed in multiple schedules.

VII. Depressants

Rohypnol®

WHAT IS ROHYPNOL®?

Rohypnol® is a trade name for flunitrazepam, a central nervous system (CNS) depressant that belongs to a class of drugs known as benzodiazepines. Flunitrazepam is also marketed as generic preparations and other trade name products outside of the United States.

Like other benzodiazepines, Rohypnol® produces sedative-hypnotic, anti-anxiety, and muscle relaxant effects. This drug has never been approved for medical use in the United States by the Food and Drug Administration. Outside the United States, Rohypnol® is commonly prescribed to treat insomnia. Rohypnol® is also referred to as a "date rape" drug.

WHAT IS ITS ORIGIN?

Rohypnol® is smuggled into the United States from other countries, such as Mexico.

What are common street names?

Common street names include:

- Circles, Forget Pill, Forget-Me-Pill, La Rocha, Lunch Money Drug, Mexican Valium, Pingus, R2, Reynolds, Roach, Roach 2, Roaches, Roachies, Roopies, Robotal, Rochas Dos, Rohypnol, Roofies, Rophies, Ropies, Roples, Row-Shay, Ruffies, and Wolfies

What does it look like?

Prior to 1997, Rohypnol® was manufactured as a white tablet (0.5-2 milligrams per tablet), and when mixed in drinks, was colorless, tasteless, and odorless. In 1997, the manufacturer responded to concerns about the drug's role in sexual assaults by reformulating the drug.

Rohypnol® is now manufactured as an oblong olive green tablet with a speckled blue core that when dissolved in light-colored drinks will dye the liquid blue. However, generic versions of the drug may not contain the blue dye.

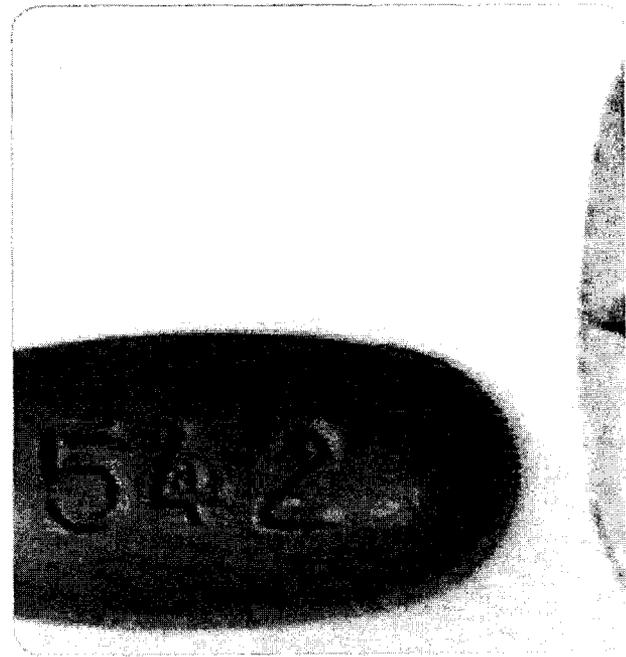
How is it abused?

The tablet can be swallowed whole, crushed and snorted, or dissolved in liquid. Adolescents may abuse Rohypnol® to produce a euphoric effect often described as a "high." While high, they experience reduced inhibitions and impaired judgment.

Rohypnol® is also abused in combination with alcohol to produce an exaggerated intoxication.

In addition, abuse of Rohypnol® may be associated with multiple-substance abuse. For example, cocaine addicts may use benzodiazepines such as Rohypnol® to relieve the side effects (e.g., irritability and agitation) associated with cocaine binges.

Rohypnol® is also misused to physically and psychologically incapacitate women targeted for sexual assault. The drug is usually placed in the alcoholic drink of an unsuspecting victim to incapacitate them and prevent resistance to sexual assault. The drug leaves the victim unaware of what has happened to them.



Rohypnol® (1)

What is its effect on the mind?

Like other benzodiazepines, Rohypnol® slows down the functioning of the CNS producing:

- Drowsiness (sedation), sleep (pharmacological hypnosis), decreased anxiety, and amnesia (no memory of events while under the influence of the substance)

Rohypnol® can also cause:

- Increased or decreased reaction time, impaired mental functioning and judgment, confusion, aggression, and excitability

What is its effect on the body?

Rohypnol® causes muscle relaxation. Adverse physical effects include:

- Slurred speech, loss of motor coordination, weakness, headache, and respiratory depression

Rohypnol also can produce physical dependence when taken regularly over a period of time.

What are its overdose effects?

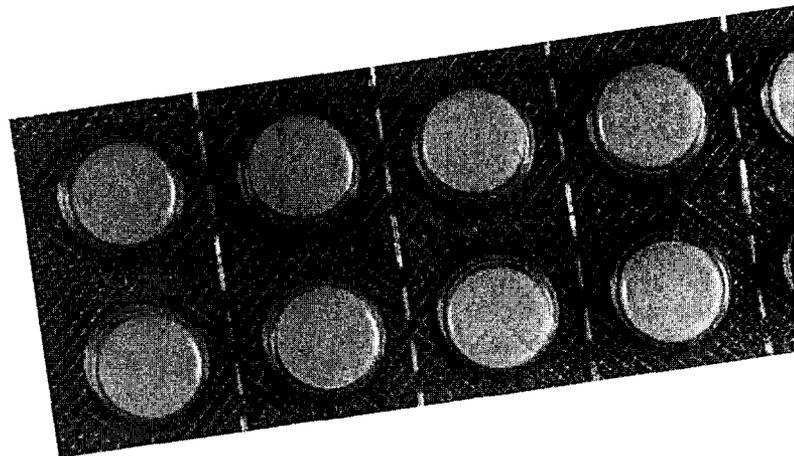
High doses of Rohypnol®, particularly when combined with CNS depressant drugs such as alcohol and heroin, can cause severe sedation, unconsciousness, slow heart rate, and suppression of respiration that may be sufficient to result in death.

Which drugs cause similar effects?

Drugs that cause similar effects include GHB (gamma hydroxybutyrate) and other benzodiazepines such as alprazolam (e.g., Xanax®), clonazepam (e.g., Klonopin®), and diazepam (e.g., Valium®).

What is its legal status in the United States?

Rohypnol® is a Schedule IV substance under the Controlled Substance Act. Rohypnol® is not approved for manufacture, sale, use or importation to the United States. It is legally manufactured and marketed in many countries. Penalties for possession, trafficking, and distribution involving one gram or more are the same as those of a Schedule I drug.



Blister pack of Rohypnol tablets



What Hallucinogens

WHAT ARE HALLUCINOGENS?

Hallucinogens are found in plants and fungi or are synthetically produced and are among the oldest known group of drugs used for their ability to alter human perception and mood.

WHAT IS THEIR ORIGIN?

Hallucinogens can be synthetically produced in illicit laboratories or are found in plants.



MDMA/ecstasy pills



LSD Blotter Sheet

What are common street names?

Common street names include:

→ Acid, Blotter, Blotter Acid, Cubes, Doses, Fry, Mind Candy, Mushrooms, Shrooms, Special K, STP, X, and XTC

What do they look like?

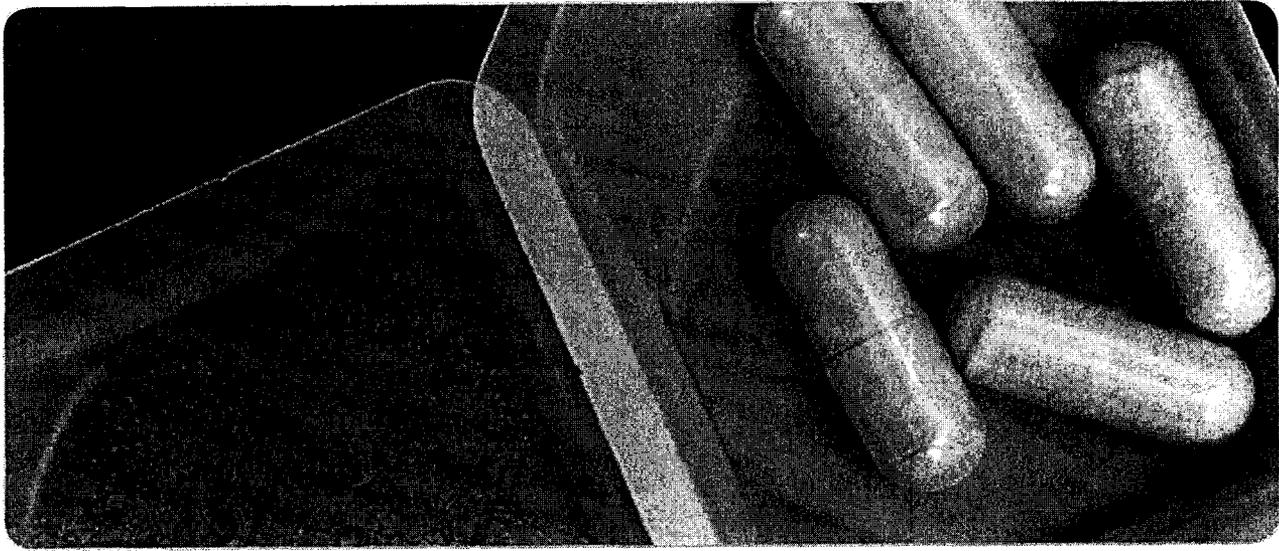
Hallucinogens come in a variety of forms. MDMA or ecstasy tablets are sold in many colors with a variety of logos to attract young abusers. LSD is sold in the form of impregnated paper (blotter acid), typically imprinted with colorful graphic designs.

How are they abused?

The most commonly abused hallucinogens among junior and senior high school students are hallucinogenic mushrooms, LSD, and MDMA or ecstasy. Hallucinogens are typically taken orally or can be smoked.

What is their effect on the mind?

Sensory effects include perceptual distortions that vary with dose, setting, and mood. Psychic effects include distortions of thought associated with time and space. Time may appear to stand still, and forms and



LSD pills and capsules

colors seem to change and take on new significance. Weeks or even months after some hallucinogens have been taken, the user may experience flashbacks — fragmentary recurrences of certain aspects of the drug experience in the absence of actually taking the drug. The occurrence of a flashback is unpredictable, but is more likely to occur during times of stress and seems to occur more frequently in younger individuals. With time, these episodes diminish and become less intense.

What is their effect on the body?

Physiological effects include elevated heart rate, increased blood pressure, and dilated pupils.

What are their overdose effects?

Deaths exclusively from acute overdose of LSD, magic mushrooms, and mescaline are extremely rare. Deaths generally occur due to suicide, accidents, and dangerous behavior, or due to the person inadvertently eating poisonous plant material.

A severe overdose of PCP and ketamine can result in:

- Respiratory depression, coma, convulsions, seizures, and death due to respiratory arrest

What is their legal status in the United States?

Many hallucinogens are Schedule I under the Controlled Substances Act, meaning that they have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.

Ecstasy/MDMA

WHAT IS ECSTASY/MDMA?

MDMA acts as both a stimulant and psychedelic, producing an energizing effect, distortions in time and perception, and enhanced enjoyment of tactile experiences.

Adolescents and young adults use it to reduce inhibitions and to promote:

→ Euphoria, feelings of closeness, empathy, and sexuality

Although MDMA is known among users as Ecstasy, researchers have determined that many Ecstasy tablets contain not only MDMA but also a number of other drugs or drug combinations that can be harmful, such as:

→ Methamphetamine, ketamine, cocaine, the over-the-counter cough suppressant dextromethorphan (DXM), the diet drug ephedrine, and caffeine

In addition, other drugs similar to MDMA, such as MDA or PMA, are often sold as Ecstasy, which can lead to overdose and death when the user takes additional doses to obtain the desired effect.

WHAT IS ITS ORIGIN?

MDMA is a synthetic chemical made in labs. Seized MDMA in the U.S. is primarily manufactured in, and smuggled across our borders from, clandestine laboratories in Canada and, to a lesser extent, the Netherlands. A small number of MDMA clandestine laboratories have also been identified operating in the U.S.

What are common street names?

Common street names include:

→ Adam, Beans, Clarity, Disco Biscuit, E, Ecstasy, Eve, Go, Hug Drug, Lover's Speed, MDMA, Peace, STP, X, and XTC

What does it look like?

MDMA is mainly distributed in tablet form. MDMA tablets are sold with logos, creating brand names for users to seek out. The colorful pills are often hidden among colorful candies. MDMA is also distributed in capsules, powder, and liquid forms.

How is it abused?

MDMA use mainly involves swallowing tablets (50-150 mg), which are sometimes crushed and snorted, occasionally smoked but rarely injected. MDMA is also available as a powder.

MDMA abusers usually take MDMA by "stacking" (taking three or more tablets at once) or by "piggy-backing" (taking a series of tablets over a short period of time). One trend among young adults is "candy flipping," which is the co-abuse of MDMA and LSD.

MDMA is considered a "party drug." As with many other drugs of abuse, MDMA is rarely used alone. It is common for users to mix MDMA with other substances, such as alcohol and marijuana.

What is its effect on the mind?

MDMA mainly affects brain cells that use the chemical serotonin to communicate with each other. Serotonin helps to regulate mood, aggression, sexual activity, sleep, and sensitivity to pain. Clinical studies suggest that MDMA may increase the risk of long-term, perhaps permanent, problems with memory and learning.

MDMA causes changes in perception, including euphoria and increased sensitivity to touch, energy, sensual and sexual arousal, need to be touched, and need for stimulation.

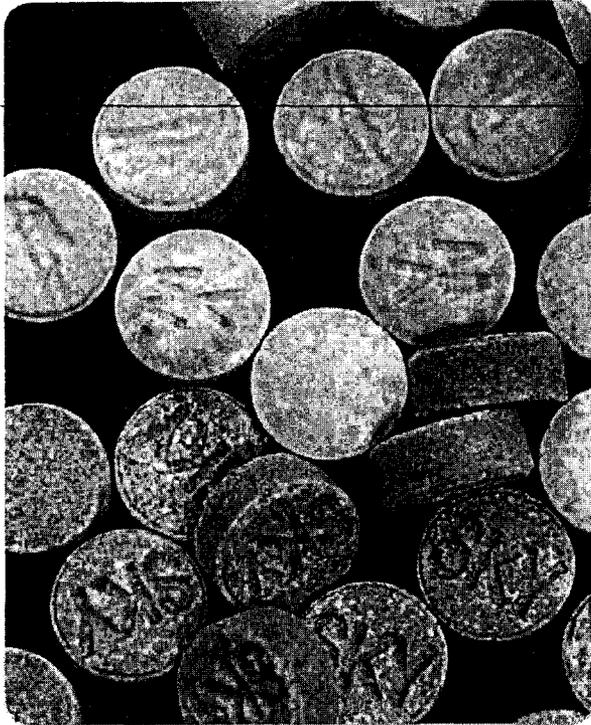
Some unwanted psychological effects include:

→ Confusion, anxiety, depression, paranoia, sleep problems, and drug craving

All these effects usually occur within 30 to 45 minutes of swallowing the drug and usually last 4 to 6 hours, but they may occur or last weeks after ingestion.

What is its effect on the body?

Users of MDMA experience many of the same effects and face many of the same risks as users of other stimulants such as cocaine and amphetamines. These include increased motor activity, alertness, heart rate, and blood pressure.



MDMA/Ecstasy pills

Some unwanted physical effects include:

→ Muscle tension, tremors, involuntary teeth clenching, muscle cramps, nausea, faintness, chills, sweating, and blurred vision

High doses of MDMA can interfere with the ability to regulate body temperature, resulting in a sharp increase in body temperature (hyperthermia), leading to liver, kidney and cardiovascular failure.

Severe dehydration can result from the combination of the drug's effects and the crowded and hot conditions in which the drug is often taken.

Studies suggest chronic use of MDMA can produce damage to the serotonin system. It is ironic that a drug that is taken to increase pleasure may cause damage that reduces a person's ability to feel pleasure.

What are its overdose effects?

In high doses, MDMA can interfere with the body's ability to regulate temperature. On occasions, this can lead to a sharp increase in body temperature (hyperthermia), resulting in liver, kidney, and cardiovascular system failure, and death. Because MDMA can interfere with its own metabolism (that is, its break down within the body), potentially harmful levels can be reached by repeated drug use within short intervals.

Which drugs cause similar effects?

No one other drug is quite like MDMA, but MDMA produces both amphetamine-like stimulation and mild mescaline-like hallucinations.

What is its legal status in the United States?

MDMA is a Schedule I drug under the Controlled Substances Act, meaning it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.

K2 / Spice

WHAT IS K2?

K2 or "Spice" is a mixture of herbs and spices that is typically sprayed with a synthetic compound chemically similar to THC, the psychoactive ingredients in marijuana. The chemical compounds typically include HU-210, HU-211, JWH-018, and JWH-073. K2 is commonly purchased in head shops, tobacco shops, various retail outlets, and over the Internet. It is often marketed as incense or "fake weed." Purchasing over the Internet can be dangerous because it is not usually known where the products come from or what amount of chemical is on the organic material.

WHAT IS ITS ORIGIN?

Manufacturers of this product are not regulated and are often unknown since these products are purchased via the Internet whether wholesale or retail. Several websites that sell the product are based in China. Some products may contain an herb called damiana, which is native to Central America, Mexico, and the Caribbean.

What are common street names?

→ Bilss, Black Mamba, Bombay Blue, Fake Weed, Genie, Spice, Zohai

What does it look like?

K2 is typically sold in small, silvery plastic bags of dried leaves and marketed as incense that can be smoked. It is said to resemble potpourri.

How is it abused?

K2 products are usually smoked in joints or pipes, but some users make it into a tea.

What is its effect on the mind?

Psychological effects are similar to those of marijuana and include paranoia, panic attacks, and giddiness.

What is its effect on the body?

Physiological effects of K2 include increased heart rate and increase of blood pressure. It appears to be stored in the body for long periods of time, and therefore the long-term effects on humans are not fully known.

What are its overdose effects?

There have been no reported deaths by overdose.

Which drugs cause similar effects?

Marijuana

What is its legal status in the United States?

On Tuesday, March 1, 2011, DEA published a final order in the Federal Register temporarily placing five synthetic cannabinoids into Schedule I of the CSA. The order became effective on March 1, 2011.

The substances placed into Schedule I are 1-pentyl-3-(1-naphthoyl) indole (JWH-018), 1-butyl-3-(1-naphthoyl) indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol; CP-47,497 C8 homologue).

This action is based on a finding by the Administrator that the placement of these synthetic cannabinoids into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. As a result of this order, the full effect of the CSA and its implementing regulations including criminal, civil and administrative penalties, sanctions, and regulatory controls of Schedule I substances will be imposed on the manufacture, distribution, possession, importation, and exportation of these synthetic cannabinoids.

Ketamine

WHAT IS KETAMINE?

Ketamine is a dissociative anesthetic that has some hallucinogenic effects. It distorts perceptions of sight and sound and makes the user feel disconnected and not in control. It is an injectable, short-acting anesthetic for use in humans and animals. It is referred to as a "dissociative anesthetic" because it makes patients feel detached from their pain and environment.

Ketamine can induce a state of sedation (feeling calm and relaxed), immobility, relief from pain, and amnesia (no memory of events while under the influence of the drug). It is abused for its ability to produce dissociative sensations and hallucinations. Ketamine has also been used to facilitate sexual assault.

WHAT IS ITS ORIGIN?

Ketamine is produced commercially in a number of countries, including the United States. Most of the ketamine illegally distributed in the United States is diverted or stolen from legitimate sources, particularly veterinary clinics, or smuggled into the United States from Mexico.

Distribution of ketamine typically occurs among friends and acquaintances, most often at raves, nightclubs, and at private parties; street sales of ketamine are rare.

What are common street names?

Common street names include:

→ Cat Tranquilizer, Cat Valium, Jet K, Kit Kat, Purple, Special K, Special La Coke, Super Acid, Super K, and Vitamin K

What does it look like?

Ketamine comes in a clear liquid and a white or off-white powder. Powdered ketamine (100 milligrams to 200 milligrams) typically is packaged in small glass vials, small plastic bags, and capsules as well as paper, glassine, or aluminum foil folds.



Vials containing liquid ketamine.

How is it abused?

Ketamine, along with the other "club drugs," has become popular among teens and young adults at dance clubs and "raves." Ketamine is manufactured commercially as a powder or liquid. Powdered ketamine is also formed from pharmaceutical ketamine by evaporating the liquid using hot plates, warming trays, or microwave ovens, a process that results in the formation of crystals, which are then ground into powder.

Powdered ketamine is cut into lines known as bumps and snorted, or it is smoked, typically in marijuana or tobacco cigarettes. Liquid ketamine is injected or mixed into drinks. Ketamine is found by itself or often in combination with MDMA, amphetamine, methamphetamine, or cocaine.

What is its effect on the mind?

Ketamine produces hallucinations. It distorts perceptions of sight and sound and makes the user feel disconnected and not in control. A "Special K" trip is touted as better than that of LSD or PCP because its hallucinatory effects are relatively short in duration, lasting approximately 30 to 60 minutes as opposed to several hours.

VIII. Hallucinogens

Slang for experiences related to Ketamine or effects of Ketamine include:

- "K-land" (refers to a mellow & colorful experience)
- "K-hole" (refers to the out-of-body, near death experience)
- "Baby food" (users sink in to blissful, infantile inertia)
- "God" (users are convinced that they have met their maker)

The onset of effects is rapid and often occurs within a few minutes of taking the drug, though taking it orally results in a slightly slower onset of effects. Flashbacks have been reported several weeks after ketamine is used. Ketamine may also cause agitation, depression, cognitive difficulties, unconsciousness, and amnesia.

What is its effect on the body?

A couple of minutes after taking the drug, the user may experience an increase in heart rate and blood pressure that gradually decreases over the next 10 to 20 minutes. Ketamine can make users unresponsive to stimuli. When in this state, users experience:

- Involuntarily rapid eye movement, dilated pupils, salivation, tear secretions, and stiffening of the muscles

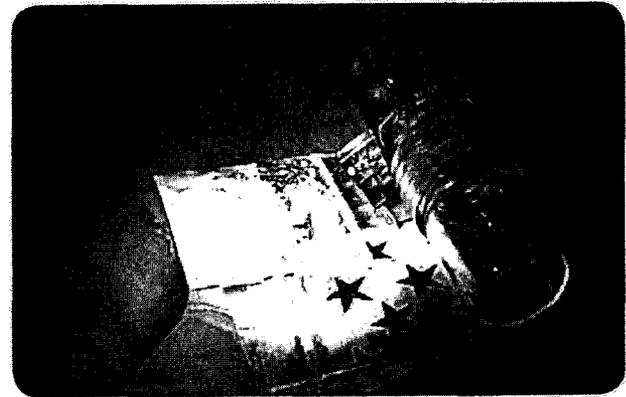
This drug can also cause nausea.

What are its overdose effects?

An overdose can cause unconsciousness and dangerously slowed breathing.

Which drugs cause similar effects?

Other hallucinogenic drugs such as LSD, PCP, and mescaline can cause hallucinations. There are also several drugs such as GHB, Rohypnol and other depressants that are misused for their amnesiac or sedative properties to facilitate sexual assault.



Ketamine in various forms

What is its legal status in the United States?

Since the 1970s, ketamine has been marketed in the United States as an injectable, short-acting anesthetic for use in humans and animals. In 1999, ketamine including its salts, isomers, and salts of isomers, became a Schedule III non-narcotic substance under the Federal Controlled Substances Act. It has a currently acceptable medical use but some potential for abuse, which may lead to moderate or low physical dependence or high psychological dependence.

LSD

WHAT IS LSD?

LSD is a potent hallucinogen that has a high potential for abuse, but currently has an accepted medical use in treatment in the United States.

WHAT IS ITS ORIGIN?

LSD is produced in clandestine laboratories in the United States.

What are common street names?

Common names for LSD include:

→ Acid, Blotter Acid, Dots, Mellow Yellow, and Window Pane

What does it look like?

LSD is sold on the street in tablets, capsules, and occasionally in liquid form. It is an odorless and colorless substance with a slightly bitter taste. LSD is often added to absorbent paper, such as blotter paper, and divided into small decorated squares, with each square representing one dose.

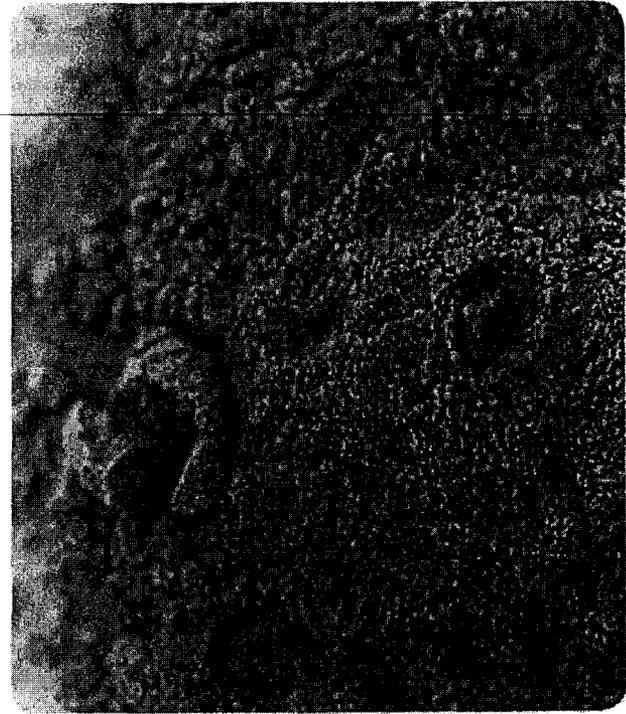
How is it abused?

LSD is abused orally.

What is its effect on the mind?

During the first hour after ingestion, users may experience visual changes with extreme changes in mood. While hallucinating, the user may suffer impaired depth and time perception accompanied by distorted perception of the shape and size of objects, movements, colors, sound, touch and the user's own body image.

The ability to make sound judgments and see common dangers is impaired, making the user susceptible to personal injury. It is possible for users to suffer acute anxiety and depression after an LSD "trip" and flashbacks have been reported days, and even months, after taking the last dose.



LSD powder

What is its effect on the body?

The physical effects include:

→ Dilated pupils, higher body temperature, increased heart rate and blood pressure, sweating, loss of appetite, sleeplessness, dry mouth, and tremors

What are its overdose effects?

Longer, more intense "trip" episodes, psychosis, and possible death

Which drugs cause similar effects?

LSD's effects are similar to other hallucinogens, such as PCP, mescaline, and peyote.

What is its legal status in the United States?

LSD is a Schedule I substance under the Controlled Substances Act, meaning that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.

VIII. Hallucinogens

Peyote & Mescaline

WHAT ARE PEYOTE AND MESCALINE?

Peyote is a small, spineless cactus. The active ingredient in peyote is the hallucinogen mescaline.

WHAT IS ITS ORIGIN?

From earliest recorded time, peyote has been used by natives in northern Mexico and the southwestern United States as a part of their religious rites. Mescaline can be extracted from peyote or produced synthetically.

What are common street names?

Common street names include:

→ Buttons, Cactus, Mesc, and Peyoto

What does it look like?

The top of the peyote cactus is referred to as the "crown" and consists of disc-shaped buttons that are cut off.

How is it abused?

The fresh or dried buttons are chewed or soaked in water to produce an intoxicating liquid. Peyote buttons may also be ground into a powder that can be placed inside gelatin capsules to be swallowed, or smoked with a leaf material such as cannabis or tobacco.

What is its effect on the mind?

Abuse of peyote and mescaline will cause varying degrees of:

→ Illusions, hallucinations, altered perception of space and time, and altered body image

Users may also experience euphoria, which is sometimes followed by feelings of anxiety.

What is its effect on the body?

Following the consumption of peyote and mescaline, users may experience:

→ Intense nausea, vomiting, dilation of the pupils, increased heart rate, increased blood pressure, a rise in body temperature that causes heavy perspiration, headaches, muscle weakness, and impaired motor coordination

Which drugs cause similar effects?

Other hallucinogens like LSD, psilocybin (mushrooms), and PCP

What is its legal status in the United States?

Peyote and Mescaline are Schedule I substances under the Controlled Substances Act, meaning that they have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.



Figure 10-10

Psilocybin

WHAT IS PSILOCYBIN?

Psilocybin is a chemical obtained from certain types of fresh or dried mushrooms.

WHAT IS ITS ORIGIN?

Psilocybin mushrooms are found in Mexico, Central America, and the United States.

What are common street names?

Common street names include:

→ Magic Mushrooms, Mushrooms, and Shrooms

What does it look like?

Mushrooms containing psilocybin are available fresh or dried and have long, slender stems topped by caps with dark gills on the underside. Fresh mushrooms have white or whitish-gray stems; the caps are dark brown around the edges and light brown or white in the center. Dried mushrooms are usually rusty brown with isolated areas of off-white.

How is it abused?

Psilocybin mushrooms are ingested orally. They may also be brewed as a tea or added to other foods to mask their bitter flavor.

What is its effect on the mind?

The psychological consequences of psilocybin use include hallucinations and an inability to discern fantasy from reality. Panic reactions and psychosis also may occur, particularly if a user ingests a large dose.

What is its effect on the body?

The physical effects include:

→ Nausea, vomiting, muscle weakness, and lack of coordination



Photo: iStockphoto.com

What are its overdose effects?

Effects of overdose include:

→ Longer, more intense "trip" episodes, psychosis, and possible death

Abuse of psilocybin mushrooms could also lead to poisoning if one of the many varieties of poisonous mushrooms is incorrectly identified as a psilocybin mushroom.

Which drugs cause similar effects?

Psilocybin effects are similar to other hallucinogens, such as mescaline and peyote.

What is its legal status in the United States?

Psilocybin is a Schedule I substance under the Controlled Substances Act, meaning that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.



IX. Marijuana/Cannabis

WHAT IS MARIJUANA?

Marijuana is a mind-altering (psychoactive) drug, produced by the *Cannabis sativa* plant. Marijuana contains over 480 constituents. THC (delta-9-tetrahydrocannabinol) is believed to be the main ingredient that produces the psychoactive effect.

WHAT IS ITS ORIGIN?

Marijuana is grown in the United States, Canada, Mexico, South America, and Asia. It can be cultivated in both outdoor and in indoor settings.

What are common street names?

Common street names include:

→ Aunt Mary, BC Bud, Blunts, Boom, Chronic, Dope, Gangster, Ganja, Grass, Hash, Herb, Hydro, Indo, Joint, Kif, Mary Jane, Mota, Pot, Reefer, Sinsemilla, Skunk, Smoke, Weed, and Yerba

What does it look like?

Marijuana is a dry, shredded green/brown mix of flowers, stems, seeds, and leaves from the *Cannabis sativa* plant. The mixture typically is green, brown, or gray in color and may resemble tobacco.

How is it abused?

Marijuana is usually smoked as a cigarette (called a joint) or in a pipe or bong. It is also smoked in blunts, which are cigars that have been emptied of tobacco and refilled with marijuana, sometimes in combination with another drug. Marijuana is also mixed with foods or brewed as a tea.

What is its effect on the mind?

When marijuana is smoked, the THC passes from the lungs and into the bloodstream, which carries the chemical to the organs throughout the body, including the brain. In the brain, the THC connects to specific sites called cannabinoid receptors on nerve cells and influences the activity of those cells.

Many of these receptors are found in the parts of the brain that influence:

→ Pleasure, memory, thought, concentration, sensory and time perception, and coordinated movement

The short-term effects of marijuana include:

→ Problems with memory and learning, distorted perception, difficulty in thinking and problem-solving, and loss of coordination

The effect of marijuana on perception and coordination are responsible for serious impairments in learning, associative processes, and psychomotor behavior (driving abilities). Long term, regular use can lead to physical dependence and withdrawal following discontinuation, as well as psychic addiction or dependence.

Clinical studies show that the physiological, psychological, and behavioral effects of marijuana vary among individuals and present a list of common responses to cannabinoids, as described in the scientific literature:

→ Dizziness, nausea, tachycardia, facial flushing, dry mouth and tremor initially

→ Merriment, happiness, and even exhilaration at high doses

→ Disinhibition, relaxation, increased sociability, and talkativeness

→ Enhanced sensory perception, giving rise to increased appreciation of music, art, and touch

- Heightened imagination leading to a subjective sense of increased creativity
- Time distortions
- Illusions, delusions, and hallucinations are rare except at high doses
- Impaired judgment, reduced coordination, and ataxia, which can impede driving ability or lead to an increase in risk-taking behavior
- Emotional lability, incongruity of affect, dysphoria, disorganized thinking, inability to converse logically, agitation, paranoia, confusion, restlessness, anxiety, drowsiness, and panic attacks may occur, especially in inexperienced users or in those who have taken a large dose
- Increased appetite and short-term memory impairment are common

Researchers have also found an association between marijuana use and an increased risk of depression, an increased risk and earlier onset of schizophrenia, and other psychotic disorders, especially for teens that have a genetic predisposition.

What is its effect on the body?

Short-term physical effects from marijuana use may include:

- Sedation, blood shot eyes, increased heart rate, coughing from lung irritation, increased appetite, and decreased blood pressure

Like tobacco smokers, marijuana smokers experience serious health problems such as bronchitis, emphysema, and bronchial asthma. Extended use may cause suppression of the immune system. Because marijuana contains toxins and carcinogens, marijuana smokers increase their risk of cancer of the head, neck, lungs, and respiratory tract.

Withdrawal from chronic use of high doses of marijuana causes physical signs including headache, shakiness, sweating, and stomach pains and nausea.

Withdrawal symptoms also include behavioral signs such as:

- Restlessness, irritability, sleep difficulties, and decreased appetite



What are its overdose effects?

No death from overdose of marijuana has been reported.

Which drugs cause similar effects?

Hashish and hashish oil are drugs made from the cannabis plant that are like marijuana, only stronger.

Hashish (hash) consists of the THC-rich resinous material of the cannabis plant, which is collected, dried, and then compressed into a variety of forms, such as balls, cakes, or cookie like sheets. Pieces are then broken off, placed in pipes or mixed with tobacco and placed in pipes or cigarettes, or smoked.

The main sources of hashish are the Middle East, North Africa, Pakistan, and Afghanistan.

Hashish Oil (hash oil, liquid hash, cannabis oil) is produced by extracting the cannabinoids from the plant material with a solvent. The color and odor of the extract will vary, depending on the solvent used. A drop or two of this liquid on a cigarette is equal to a single marijuana joint. Like marijuana, hashish and hashish oil are both Schedule I drugs.

What is its legal status in the United States?

Marijuana is a Schedule I substance under the Controlled Substances Act, meaning that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.

Marinol, a synthetic version of THC, the active ingredient found in the marijuana plant, can be prescribed for the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer and to stimulate appetite in AIDS patients. Marinol is a Schedule III substance under the Controlled Substances Act.

What is their effect on the mind?

Case studies and scientific research indicate that high doses of anabolic steroids may cause mood and behavioral effects.

In some individuals, steroid use can cause dramatic mood swings, increased feelings of hostility, impaired judgment, and increased levels of aggression (often referred to as "roid rage")

When users stop taking steroids, they may experience depression that may be severe enough to lead one to commit suicide.

Anabolic steroid use may also cause psychological dependence and addiction.

What is their effect on the body?

A wide range of adverse effects is associated with the use or abuse of anabolic steroids. These effects depend on several factors including:

→ Age, sex, the anabolic steroid used, amount used, and duration of use

In adolescents, anabolic steroid use can stunt the ultimate height that an individual achieves.

In boys, steroid use can cause early sexual development, acne, and stunted growth.

In adolescent girls and women, anabolic steroid use can induce permanent physical changes, such as deepening of the voice, increased facial and body hair growth, menstrual irregularities, male pattern baldness, and lengthening of the clitoris.

In men, anabolic steroid use can cause shrinkage of the testicles, reduced sperm count, enlargement of the male breast tissue, sterility, and an increased risk of prostate cancer.

In both men and women, anabolic steroid use can cause high cholesterol levels, which may increase the risk of coronary artery disease, strokes, and heart attacks. Anabolic steroid use can also cause acne and fluid retention. Oral preparations of anabolic steroids, in particular, can damage the liver.

Abusers who inject steroids run the risk of contracting various infections due to non-sterile injection techniques, sharing of contaminated needles, and the use of steroid preparations manufactured in non-sterile environments. All these factors put

users at risk for contracting viral infections such as HIV/AIDS or hepatitis B or C, and bacterial infections at the sight of injection.

Abusers may also develop endocarditis, a bacterial infection that causes a potentially fatal inflammation of the heart lining.

What are their overdose effects?

Anabolic steroids are not associated with overdoses. The adverse effects a user would experience develop from the use of steroids over time.

Which drugs cause similar effects?

There are several substances that produce effects similar to those of anabolic steroids. These include human growth hormone (hHG), clenbuterol, gonadotropins, and erythropoietin.

What is their legal status in the United States?

Anabolic steroids are Schedule III substances under the Controlled Substances Act. Only a small number of anabolic steroids are approved for either human or veterinary use. Steroids may be prescribed by a licensed physician for the treatment of testosterone deficiency, delayed puberty, low red blood cell count, breast cancer, and tissue wasting resulting from AIDS.



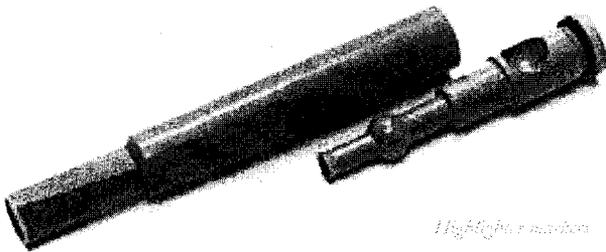
XI. Inhalants

WHAT ARE INHALANTS?

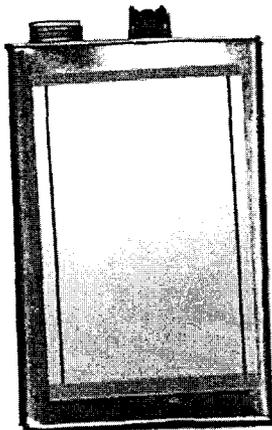
Inhalants are invisible, volatile substances found in common household products that produce chemical vapors that are inhaled to induce psychoactive or mind altering effects.

WHAT IS THEIR ORIGIN?

There are more than 1,000 products that are very dangerous when inhaled — things like typewriter correction fluid, air conditioning refrigerant, felt tip markers, spray paint, air freshener, butane, and even cooking spray. See products abused as inhalants at www.inhalants.org/product.htm (National Inhalant Prevention Coalition).



Highlighter marker



Lighter

What are common street names?

Common street names include:

→ Gluey, Huff, Rush, and Whippets

What do they look like?

Common household products such as glue, lighter fluid, cleaning fluids, and paint all produce chemical vapors that can be inhaled.

How are they abused?

Although other abused substances can be inhaled, the term "inhalants" is used to describe a variety of substances whose main common characteristic is that they are rarely, if ever, taken by any route other than inhalation.

Inhalants are breathed in through the nose or the mouth in a variety of ways, such as:

→ "Sniffing" or "snorting"

→ "Bagging" — sniffing or inhaling fumes from substances sprayed or deposited inside a plastic or paper bag

→ "Huffing" from an inhalant-soaked rag stuffed in the mouth, or inhaling from balloons filled with nitrous oxide

Inhalants are often among the first drugs that young children use. About 1 in 5 kids report having used inhalants by the eighth grade. Inhalants are also one of the few substances abused more by younger children than by older ones.

What is their effect on the mind?

Inhalant abuse can cause damage to the parts of the brain that control thinking, moving, seeing, and hearing. Cognitive abnormalities can range from mild impairment to severe dementia.

What is their effect on the body?

Inhaled chemicals are rapidly absorbed through the lungs into the bloodstream and quickly distributed to the brain and other organs. Nearly all inhalants produce effects similar to anesthetics, which slow down the body's function. Depending on the degree of abuse, the user can experience slight stimulation, feeling of less inhibition or loss of consciousness.

Within minutes of inhalation, the user experiences intoxication along with other effects similar to those produced by alcohol. These effects may include slurred speech, an inability to coordinate movements, euphoria, and dizziness. After heavy use of inhalants, abusers may feel drowsy for several hours and experience a lingering headache.

Additional symptoms exhibited by long-term inhalant abusers include:

→ Weight loss, muscle weakness, disorientation, inattentiveness, lack of coordination, irritability, depression, and damage to the nervous system and other organs

Some of the damaging effects to the body may be at least partially reversible when inhalant abuse is stopped; however, many of the effects from prolonged abuse are irreversible.

Prolonged sniffing of the highly concentrated chemicals in solvents or aerosol sprays can induce irregular and rapid heart rhythms and lead to heart failure and death within minutes.

There is a common link between inhalant use and problems in school — failing grades, chronic absences, and general apathy.

Other signs include:

→ Paint or stains on body or clothing; spots or sores around the mouth; red or runny eyes or nose; chemical breath odor; drunk, dazed, or dizzy appearance; nausea; loss of appetite; anxiety; excitability; and irritability

What are their overdose effects?

Because intoxication lasts only a few minutes, abusers try to prolong the high by continuing to inhale repeatedly over the course of several hours, which is a very dangerous practice. With successive inhalations, abusers may suffer loss of consciousness and/or death.

"Sudden sniffing death" can result from a single session of inhalant use by an otherwise healthy young person. Sudden sniffing death is particularly associated with the abuse of butane, propane, and chemicals in aerosols.

Inhalant abuse can also cause death by asphyxiation from repeated inhalations, which lead to high concentrations of inhaled fumes displacing the available oxygen in the lungs, suffocation by blocking air from entering the lungs when inhaling fumes from a plastic bag placed over the head, and choking from swallowing vomit after inhaling substances.

Which drugs cause similar effects?

Most inhalants produce a rapid high that is similar to the effects of alcohol intoxication.

What is their legal status in the United States?

The common household products that are misused as inhalants are legally available for their intended and legitimate uses. Many state legislatures have attempted to deter youth who buy legal products to get high by placing restriction on the sale of these products to minors.



XII. Drugs of Concern

Even though some substances are not currently controlled by the Controlled Substances Act, they pose risks to individuals who abuse them. The following section describes these drugs of concern and their associated risks.

Bath Salts or Designer Cathinones (*Synthetic Stimulants*)

WHAT ARE "BATH SALTS?"

Synthetic stimulants that are marketed as "bath salts" are often found in a number of retail products. These synthetic stimulants are chemicals. The chemicals are synthetic derivatives of cathinone, a central nervous system stimulant, which is an active chemical found naturally in the khat plant. Mephedrone and MDPV (3-4 methylenedioxypyrovalerone) are two of the designer cathinones most commonly found in these "bath salt" products. Many of these products are sold over the Internet, in convenience stores, and in "head shops."



Bath salts

WHAT IS THEIR ORIGIN?

Law enforcement officials believe that the stimulant chemicals contained in these products are manufactured in China and India and packaged for wholesale distribution in Eastern Europe. Many countries have banned these products.

What are common street names?

→ Bliss, Blue Silk, Cloud Nine, Drone, Energy-1, Ivory Wave, Lunar Wave, Meow Meow, Ocean Burst, Pure Ivory, Purple Wave, Red Dove, Snow Leopard, Stardust, Vanilla Sky, White Dove, White Knight, White Lightening

What does it look like?

"Bath salt" stimulant products are sold in powder form in small plastic or foil packages of 200 and 500 milligrams under various brand names. Mephedrone is a fine white, off-white, or slightly yellow-colored powder. It can also be found in tablet and capsule form. MDPV is a fine white or off-white powder.

How is it abused?

"Bath salts" are usually ingested by sniffing/snorting. They can also be taken orally, smoked, or put into a solution and injected into veins.

What is their effect on the mind?

People who abuse these substances have reported agitation, insomnia, irritability, dizziness, depression, paranoia, delusions, suicidal thoughts, seizures, and panic attacks. Users have also reported effects including impaired perception of reality, reduced motor control, and decreased ability to think clearly.

What is their effect on the body?

Cathinone derivatives act as central nervous system stimulants causing rapid heart rate (which may lead to heart attacks and strokes), chest pains, nosebleeds, sweating, nausea, and vomiting.

What are their overdose effects?

These substances are usually marketed with the warning "not intended for human consumption." Any time that users put uncontrolled or unregulated substances into their bodies, the effects are unknown and can be dangerous.

Which drugs cause similar effects?

→ Amphetamine, Cocaine, Khat, LSD, MDMA

What is their legal status in the United States?

Mephedrone has no approved medical use in the United States. It is not specifically scheduled under the Controlled Substances Act, but it is a chemical analogue of methcathinone, which is a Schedule I controlled substance. Incidents involving mephedrone can be prosecuted under the Federal Analog Act of the Controlled Substances Act. MDPV (3,4-methylenedioxypropylrovalerone) has no approved medical use in the United States. MDPV is not scheduled under the CSA.

XII. Drugs of Concern

DXM

WHAT IS DXM?

DXM is a cough suppressor found in more than 120 over-the-counter (OTC) cold medications, either alone or in combination with other drugs such as analgesics (e.g., acetaminophen), antihistamines (e.g., chlorpheniramine), decongestants (e.g., pseudoephedrine), and/or expectorants (e.g., guaifenesin). The typical adult dose for cough is 15 or 30 mg taken three to four times daily. The cough-suppressing effects of DXM persist for 5 to 6 hours after ingestion. When taken as directed, side-effects are rarely observed.

WHAT IS ITS ORIGIN?

DXM abusers can obtain the drug at almost any pharmacy or supermarket, seeking out the products with the highest concentration of the drug from among all the OTC cough and cold remedies that contain it. DXM products and powder can also be purchased on the Internet.

What are common street names?

Common street names include:

→ CCC, Dex, DXM, Poor Man's PCP, Robo, Rojo, Skittles, Triple C, and Velvet

What does it look like?

DXM can come in the form of:

→ Cough syrup, tablets, capsules, or powder

How is it abused?

DXM is abused in high doses to experience euphoria and visual and auditory hallucinations. Abusers take various amounts depending on their body weight and the effect they are attempting to achieve. Some abusers ingest 250 to 1,500 milligrams in a single dosage, far more than the recommended therapeutic dosages described above.



DXM powder

Illicit use of DXM is referred to on the street as "Robo-tripping," "skittling," or "dexing." The first two terms are derived from the products that are most commonly abused, Robitussin and Coricidin HBP. DXM abuse has traditionally involved drinking large volumes of the OTC liquid cough preparations. More recently, however, abuse of tablet and gel capsule preparations has increased.

These newer, high-dose DXM products have particular appeal for abusers. They are much easier to consume, eliminate the need to drink large volumes of unpleasant-tasting syrup, and are easily portable and concealed, allowing an abuser to continue to abuse DXM throughout the day, whether at school or work.

DXM powder, sold over the Internet, is also a source of DXM for abuse. (The powdered form of DXM poses additional risks to the abuser due to the uncertainty of composition and dose.)

DXM is also distributed in illicitly manufactured tablets containing only DXM or mixed with other drugs such as pseudoephedrine and/or methamphetamine.

DXM is abused by individuals of all ages, but its abuse by teenagers and young adults is of particular concern. This abuse

is fueled by DXM's OTC availability and extensive "how to" abuse information on various web sites.

What is its effect on the mind?

Some of the many psychoactive effects associated with high-dose DXM include:

- Confusion, inappropriate laughter, agitation, paranoia, and hallucinations

Other sensory changes, including the feeling of floating and changes in hearing and touch

Long-term abuse of DXM is associated with severe psychological dependence. Abusers of DXM describe the following four dose-dependent "plateaus":

PLATEAU	DOSE (MG)	SENSATION
1st	100 - 200	Mild stimulation
2nd	200 - 400	Euphoria and hallucinations
3rd	300 - 600	Distorted visual perceptions Loss of motor coordination
4th	500 - 1500	Out-of-body sensations

What is its effect on the body?

DXM intoxication involves:

- Over-excitability, lethargy, loss of coordination, slurred speech, sweating, hypertension, and involuntary spasmodic movement of the eyeballs

The use of high doses of DXM in combination with alcohol or other drugs is particularly dangerous, and deaths have been reported. Approximately 5-10% of Caucasians are poor DXM metabolizers and at increased risk for overdoses and deaths. DXM taken with antidepressants can be life threatening.

OTC products that contain DXM often contain other ingredients such as acetaminophen, chlorpheniramine, and guaifenesin that have their own effects, such as:

- Liver damage, rapid heart rate, lack of coordination, vomiting, seizures, and coma

To circumvent the many side effects associated with these other ingredients, a simple chemical extraction procedure has been developed and published on the Internet that removes most of these other ingredients in cough syrup.

What are its overdose effects?

DXM overdose can be treated in an emergency room setting and generally does not result in severe medical consequences or death. Most DXM-related deaths are caused by ingesting the drug in combination with other drugs. DXM-related deaths also occur from impairment of the senses, which can lead to accidents.

In 2003, a 14-year-old boy in Colorado who abused DXM died when he was hit by two cars as he attempted to cross a highway. State law enforcement investigators suspect that the drug affected the boy's depth perception and caused him to misjudge the distance and speed of the oncoming vehicles.

Which drugs cause similar effects?

Depending on the dose, DXM can have effects similar to marijuana or Ecstasy. In high doses its out-of-body effects are similar to those of Ketamine or PCP.

What is its legal status in the United States?

DXM is a legally marketed cough suppressant that is neither a controlled substance nor a regulated chemical under the Controlled Substances Act.

XII. Drugs of Concern

Salvia Divinorum

WHAT IS SALVIA DIVINORUM?

Salvia divinorum is a perennial herb in the mint family that is abused for its hallucinogenic effects.

WHAT IS ITS ORIGIN?

Salvia is native to certain areas of the Sierra Mazateca region of Oaxaca, Mexico. It is one of several plants that are used by Mazatec Indians for ritual divination. Salvia divinorum plants can be grown successfully outside of this region. They can be grown indoors and outdoors, especially in humid semitropical climates.

What are common street names?

Common street names include:

→ Maria Pastora, Sally-D, and Salvia

What does it look like?

The plant has spade-shaped variegated green leaves that look similar to mint. The plants themselves grow to more than three feet high, have large green leaves, hollow square stems, and white flowers with purple calyces.

How is it abused?

Salvia can be chewed, smoked, or vaporized.

What is its effect on the mind?

Psychic effects include perceptions of bright lights, vivid colors, shapes, and body movement, as well as body or object distortions. Salvia divinorum may also cause fear and panic, uncontrollable laughter, a sense of overlapping realities, and hallucinations.

Salvinorin A is believed to be the ingredient responsible for the psychoactive effects of Salvia divinorum.

What is its effect on the body?

Adverse physical effects may include:

→ Loss of coordination, dizziness, and slurred speech

What are its overdose effects?

Adverse physical effects may include lack of coordination, dizziness, and slurred speech.

Which drugs cause similar effects?

When Salvia divinorum is chewed or smoked, the hallucinogenic effects elicited are similar to those induced by other Schedule hallucinogenic substances.

What is its legal status in the United States?

Neither Salvia divinorum nor its active constituent Salvinorin A has an approved medical use in the United States. Salvia is not controlled under the Controlled Substances Act. Salvia divinorum is, however, controlled by a number of states. Since Salvia is not controlled by the CSA, some online botanical companies and drug promotional sites have advertised Salvia as a legal alternative to other plant hallucinogens like mescaline.



Salvia divinorum (Salvia divinorum)

XIII. Resources

DRUG PREVENTION RESOURCES

Drug prevention programs are designed and implemented on many levels. The federal government has instituted a number of national drug prevention programs which reach targeted populations through public service announcements, grant programs, educational programs and the sharing of expertise. State and local governments also have a significant number of prevention programs which are tailored to address particular problems and needs. Law enforcement and the military have brought drug prevention expertise into classrooms and communities; businesses have also contributed significantly to drug prevention through sponsored programs, drug-free policies and corporate support for community initiatives. Other segments of society, including faith-based institutions, civic organizations, and private foundations are also active forces in drug prevention.

Below is a partial list of drug prevention agencies and programs. There are many other outstanding efforts which are ongoing across the nation; it is impossible to include them all. Some programs are aimed at particular populations or specific drugs. Within a given agency, there may be many prevention programs which are aimed at different audiences.

FEDERAL DRUG PREVENTION AGENCIES AND PROGRAMS:

Drug Enforcement Administration (DEA):

In addition to dismantling the major drug trafficking organizations, DEA is committed to reducing the demand for drugs in America. DEA's Demand Reduction Program is carried out by Special Agents across the United States who work in communities to share expertise and information on drug trends, emerging problems, and the dangers of drugs.

→ www.dea.gov

→ www.JustThinkTwice.com

→ www.GetSmartAboutDrugs.com

Office of National Drug Control Policy (ONDCP):

This office reports to the President of the United States. ONDCP administers the Youth Anti-Drug Media Campaign.

→ www.mediacampaign.org

→ www.whitehousedrugpolicy.gov

Substance Abuse and Mental Health Services Administration (SAMHSA):

This organization is responsible for overseeing and administering mental health, drug prevention, and drug treatment programs around the nation. The Center for Substance Abuse Prevention (CSAP) and the Center for Substance Abuse Treatment (CSAT) are part of SAMHSA.

→ www.samhsa.gov

→ www.samhsa.gov/prevention

→ www.samhsa.gov/about/csap.aspx

U.S. Department of Education (ED):

ED has many anti-drug programs.

→ www.ed.gov

National Institute on Drug Abuse (NIDA):

NIDA conducts and disseminates the results of research about the effects of drugs on the body and the brain. NIDA is an excellent source of information on drug addiction.

→ www.nida.nih.gov

National Guard:

The National Guard provides drug education to communities in all 50 states.

→ www.ngb.army.mil

Weed and Seed:

Operation Weed and Seed is a strategy to prevent and reduce violent crime, drug abuse, and gang activity in targeted high-crime neighborhood. Law enforcement agencies and prosecutors cooperate in "weeding out" criminals and "seeding" to bring in human services, prevention intervention, treatment, and neighborhood revitalization.

→ www.ojp.usdoj.gov/ccdo/ws/welcome.html

Other Anti-Drug Organizations:

National Association of State Alcohol and Drug Abuse Directors (NASADAD)

→ www.nasadad.org

Community Anti-Drug Coalitions Of America (CADCA)

→ www.cadca.org

National Crime Prevention Council (NCPC)

→ www.ncpc.org

National Families in Action (NFIA)

→ www.nationalfamilies.org

You can obtain free anti-drug information from:

National Clearinghouse for Alcohol and Drug Information (NCADI)

→ www.health.org

The National Center on Addiction and Substance Abuse at Columbia University (CASA)

→ www.casacolumbia.org

Elks Drug Awareness Program

→ www.elks.org/dap

Partnership for a Drug-Free America (PDFA)

→ www.drugfree.org

Scott Newman Center

→ www.scottnewmancenter.org

American Council for Drug Education (ACDE)

→ www.acde.org

Drug Strategies

→ www.drugstrategies.org

Youth Anti-Drug Organizations:

Learning For Life

→ www.learning-for-life.org

PRIDE Youth Programs

→ www.prideyouthprograms.org

Drug Abuse Resistance Education (DARE America) (DARE)

→ www.dare.com

Students Against Destructive Decisions (SADD)

→ www.sadd.org

Law Enforcement Exploring

→ www.learning-for-life.org/exploring/lawenforcement/

Notes

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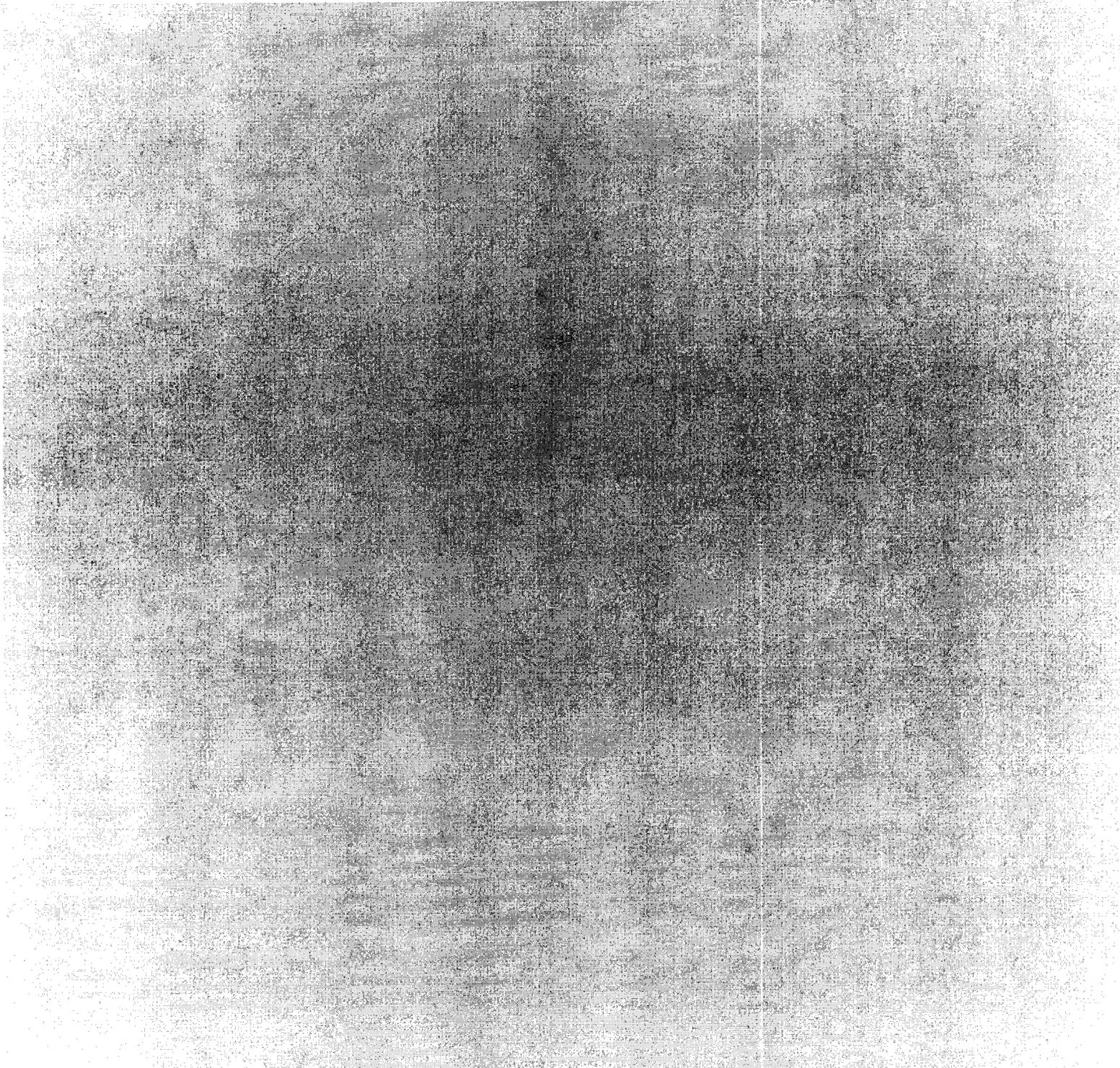


GetSmartAboutDrugs
A DEA Resource for Parents

www.GetSmartAboutDrugs.com



www.JustThinkTwice.com



Pyrovalerone analogues such as MDPV are potent inhibitors of the dopamine and norepinephrine transporters... yet, shows minimal inhibition of the serotonin transporter.

The potency of pyrovalerone for dopamine uptake and norepinephrine uptake is 9-fold and 13-fold more potent than cocaine, respectively.⁽³⁾

↳ Meltzer et al.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) analogues: a promising class of monoamine uptake inhibitors.
J Med. Chem 2006; 49: 1420-1432.

Interestingly, it is noted that:

The mechanism of hyperthermia in MDPV has not been elucidated but can be extrapolated from other similar xenobiotic compounds.

NE, dopa. ± serotonin have all been implicated in normal hypothalamic control of thermogenesis.

It was reported that there is scant available clinical information in the medical literature on both salt abuse.

Drug induced psychosis and aggression appear to be more severe than with other amphetamine-like stimulants.^{10, 11.}

Authors report that with limited available clinical data, the management of MDPV intoxication should be similar to the management of other sympathomimetic agents such as cocaine.

MDCM - Michigan Dept. of Community Health

2-

PCC - Michigan Poison Control Centre

(7)

Anon. 2011. Emergency Department visits after use of a drug sold as "Bath Salts" - Michigan, Nov. 13, 2010 - Mar. 31, 2011.

Morbidity and Mortality Weekly Report. 60(19): 624-627.

Michigan Poison C.C. told Mich. Dept. of Com. Health... (Feb 1, 2011) of ED visits in Marquette City.

This report summarizes the subsequent investigation which identified 35 persons who had ingested, inhaled or injected "bath salts" and visited a Michigan ED during Nov. 13, 2010 - Mar 31, 2011.

Among the 35 patients, the most common signs and symptoms of toxicity were agitation, tachycardia, delusions/hallucinations.

17 patients were hospitalized, and one was dead* upon arrival of ED.

Reason. Emergency public health order to remove the toxic "bath salts" from the marketplace.

From Nov 2010 to Jan 2011, the Marquette County ED, treated seven (7) patients who arrived at the ED w/ hypertension, tachycardia, tremors, motor automatisms, mydriasis, delusions and paranoia.

Some patients were violent, requiring restraint and increased demand on ED staff members. Responding also placed middle or law enforcement in foster care as many patients had young children who needed care while their parents were incapacitated.

Patients reported using "bath salts" for a *20 package and labelled "not intended for human consumption".

By Feb. 3, a total of 13 cases in Marquette County, and one fatality had been reported to the PCC.

* Marquette County issued Emergency public health order on Feb 4 Health Dept.

Products seized by law enforcement from proprietor of the store
contained MDPV (White Rush).

Concurrently, REC had become aware of 2 cases elsewhere
in the State.

On Feb 5, (NOCH) used its chemical poisoning reg.
to mandate statewide reporting by hospitals of cases of
possible "bath salts" intoxication so that cases
could be identified & characterized.

A case was defined as: "a person who visited a Michigan ED
during Nov 13, 2010 - Mar 31, 2011, after self-reported or
suspected use of "bath salts," & with cardiovascular, neurologic,
or psychological signs or symptoms, consistent with acute intoxication."

Michigan ED admissions ^{3 -} Nov 13, 2010 - Mar 31, 2011

N=35 Breakdown as follows:

3/35 had visited ED NR for 'bath salts' abuse

Patients: age 20-55 (med. 28.5 yrs).

As of May 16, 2011
71 ED visits by 65 patients had been reported in Michigan since Nov 13, 2010.

19/35 (54%) were men σ

16/35 (46%) were women ϕ

24/35 (69%) had a self-reported history of drug abuse.

11/35 (31%) reporting polysubstance abuse

12/35 (34%) reporting i.v. use

(assume 23/35 other routes ingestion & / or inhalation).

Interestingly ...

16/35 (46%) had a history of mental illness

(e.g. bipolar disorder, schizophrenia or depression) in their medical records and six had suicidal thoughts or suspected attempts that might have been related to "bath salts" abuse.

n=27 (77%) occurred in Michigan's Upper Peninsula Region, with n=16 cases (51%) occurring in Marquette County.

n=10 Ten. (12%) of Michigan's 83 counties reported cases.

Clinical Findings were consistent with intoxication w/ stimulants.

Of the 35 patients, 32 (91%) had neurologic*
27 (77%) had cardiovascular
17 (49%) had psychological symptoms

* n= 17 patients were hospitalized
n= 15 were treated and released from the ED.
n= 2 left ED against medical advice
n= 1 was dead upon arrival

n: 35 { 22 (63%) had injected the drug
9 (26%) had snorted it
4 (11%) had ingested it

* n: 5 (14%) → she includes the patient who died

↳ the exposure route was unknown.

n: 5 → had had multiple exposure routes

No relationship was found between the exposure route and severity of illness. *

Of the 17 patients in known drug test results, 16 (94%) tested positive for other drugs (e.g. marijuana, opiates, benzos, cocaine or amphetamines).

Toxicology results for the person who died revealed a high level of MDPV, along with marijuana and prescription drugs.

< Autopsy results revealed MDPV toxicity to be the primary factor contributing to death >

↳ The manner of death was ruled accidental, consistent with an attempt to get high

Of the 17 hospitalized persons...

9 were admitted to the Intensive Care Unit (ICU).

(5 were admitted to a general floor and;

3 were admitted directly to a psychiatric unit.

74/9 → were admitted directly to a psychiatric unit.

↳ Treatment included benzos (such as lorazepam) toxicity. (low or med. doses were sufficient).

(4)

(16)

Muzile et al. 2012. Serotonin syndrome associated with MDPV use: a case report. *Annals of Emergency Medicine*. 60(1): 105-102

Case report:

41 yr old
A woman → developed clinical findings consistent with serotonin syndrome after insufflation of MDPV.

MDPV belongs to a group of substances called, phenylethylamines, β -ketone analogs of other drugs of abuse, such as amphetamines and 3,4-methylenedioxymethamphetamine.

Blood pressure 99/64 mmHg

Pulse rate 78 beats/min

Temp. 98.1 °F - was alert, oriented ~~but~~ agitated.

↳ Eight hours after arrival

- she became agitated, she started hallucinating,
- developed a temp. of 104.2 °F with a blood pressure of 152/85 mmHg and a pulse rate of 130 beats/min.

She received 13mg of lorazepam and 5mg of diazepam, w/o improvements of her symptoms.

↳ Blood EtOH level was 23 mg/dL.

This patient met the ["]Hunter["] criteria for serotonin syndrome.

The Hunter Serotonin Toxicity criteria suggest serotonin syndrome if a patient has ingested a serotonergic agent and meets one of the following:

- (1) spontaneous clonus
- (2) inducible or ocular clonus with agitation or diaphoresis.
- (3) tremor, hyperreflexia
- (4) muscle rigidity, hyperthermia and ocular or inducible clonus.

The diagnosis of serotonin syndrome is entirely clinical and it is believed that

1. the presence of severe agitation, tachycardia, hypertension, hyperthermia, (lower extremity rigidity), hyperreflexia and inducible clonus, responsive to (GABA) gamma-aminobutyric acid agonists and cyproheptadine (when other causes unlikely) is diagnostic of serotonin syndrome.

Many substances have been implicated in serotonin syndrome, including analgesics such as meperidine and tramadol, synthetic substances such as ecstasy & methamphetamine and most antidepressants.

Serotonin syndrome has been associated with structural analogues of MDPV including MDMA and mephedrone.

Although the pharmacology data of MDPV are incomplete, many postulate that, according to existing studies, phenethylamines marketed as bath salts, have properties similar to high-stimulated MDMA.⁹¹

Kraikku et al. 2011. New designer drug of abuse: 3,4-methylene
dioxypyrovalerone (MDPV). Findings from apprehended
drivers in Finland.

↳ this paper is already reported in IAS summary.

Other interesting data reported:

At higher doses → some users report extremely unpleasant "come-down" effects.

74



Re: MDPV 
Nathan Isotalo to: Tara Phillips

2012-03-09 01:21 PM

Hi Tara,

please find attached a draft IAS for MDPV. Next steps would include CSSWG endorsement, triage and scheduling regulatory proposal development.

Nathan.



Draft Bath Salt (MDPV) Scheduling IAS Mar 9 2012.doc

Tara Phillips

From: Tara Phillips/HC-SC/GC/CA To: Nathan I...

2012-03-08 11:24:52 AM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-03-08 11:24 AM
Subject: Can you pls come see me about bath salts when you have a minute?

Issue Analysis Summary

Regulation of 3,4-methylenedioxypropylamphetamine (MDPV)

Regulatory Policy Division

Office of Controlled Substances

Controlled Substances and Tobacco Directorate

March 9, 2012

CONTENTS

1. APPROVALS
2. ISSUE
3. PURPOSE
4. CONTEXT
5. ASSESSMENT OF RISKS AND BENEFITS
6. IDENTIFICATION AND ANALYSIS OF OPTIONS
7. CONSULTATIONS
8. CONSIDERATIONS
9. RECOMMENDATION
10. IMPLEMENTATION AND EVALUATION

Disclaimer: This Issue Analysis Summary (IAS) contains "commercial confidential scientific, technical, trade secret, sensitive information" provided by sponsor Janssen-Ortho Inc. Not for disclosure without consent of the owner.

1. APPROVALS

This Issue Analysis Summary is considered approved.

Johanne Beaulieu, Director
Office of Controlled Substances
Controlled Substances and Tobacco Directorate

[DD/MM/YYYY]

2. ISSUE

Over the past couple of years, in North America, abuse of a new designer drug “bath salts” has steadily been increasing (Borek and Holstege, 2012; Kyle et al., 2011). Substance abuse and police/border seizures of Internet marketed products known as “bath salts” has risen sharply in the United States the past few years and is slowly on the rise in Canada however, does not yet point to widespread use of “bath salt” products in the general population.

Laboratory analysis has shown that these products may contain either mephedrone and/or 3,4-methylenedioxypyrovalerone (MDPV) and are often labeled as, “not for human consumption.” These products are abused for their stimulant effects from swallowing, smoking, snorting, rectal administration or the injection of them.

Reported adverse effects of abused bath salt products include: teeth grinding, sweating, hypertension, paranoia, delusions, hallucinations, tachycardia, serotonin syndrome, insomnia, psychosis, suicidal thoughts, self-harmful tendencies such as self-mutilation and in some cases death (Kyle et al. 2011; Murray et al. 2012; Mugele et al. 2012).

For these reasons they may pose significant risks to public safety, security and health of Canadians and for this reason an assessment of “bath salts” has been carried out below.

Mephedrone or 4-methylmethcathinone was identified by a Health Canada status decision as an analogue of cathinone, a Schedule III listed controlled substance under the *Controlled Drugs and Substances Act* (CDSA). Cathinone is a naturally occurring β -ketone amphetamine analogue found in the leaves of the *Catha edulis* plant. Synthetic cathinones like mephedrone are derivatives of this compound.

This assessment relates to the scheduling of MDPV.

3. PURPOSE

To assess MDPV against the criteria for the addition of a substance to one of the Schedules to the CDSA, and thus determine whether it should be regulated as a controlled substance in Canada. This objective aligns with the Government of Canada's objective of restricting access to substances which may cause harm to individuals or society when diverted or misused.

4. CONTEXT

4.1 Legislative Frameworks

As "bath salts" in this case are not traditional epsom salt (magnesium sulphate) bath salt consumer products that fall under the definition of consumer product of the *Consumer Product Safety Act* (CPSA) but are new designer drug products that look like epsom salts however have a very different composition. They may contain the controlled substances, mephedrone and methylone and therefore such products are illegal in Canada as they fall under the legislative mandate of the CDSA.

4.1.1 Controlled Drugs and Substances Act and its Regulations

The CDSA provides a legislative framework for the control of substances that can alter mental processes and may produce harm to the health of an individual or to society when diverted or misused. Except as authorized under regulation, activities such as possession, trafficking, importation, exportation, possession for the purpose of trafficking or exportation, and the production of controlled substances are prohibited under the CDSA.

The CDSA and its regulations seek to support access to controlled substances for medical and scientific purposes while minimizing their diversion for illicit purposes. Controlled substances are captured under Schedule I to V of the CDSA. Drug offence contraventions under the CDSA carry penalties of varying severity described in Part I of the CDSA. Offences associated with Schedule IV are similar to those associated with substances in Schedule I, II and III except that there is no offence for simple possession.

When a substance is being considered for addition to one of the Schedules to the CDSA by the Office of Controlled Substances, Controlled Substances and Tobacco Directorate, Healthy Environments and Consumer Safety Branch, Health Canada, several factors are assessed, as follows:

- International requirements and trends in control and/or scheduling;
- Chemical and/or pharmacological similarity to substances listed in the Schedules to the CDSA;
- Legitimate use of the substance, including therapeutic, scientific, industrial and commercial uses;
- Potential for abuse and/or addiction liability;
- Evidence of extent of actual abuse in Canada and internationally; and,
- Risk to personal and public health and safety.

4.2 Assessment of Bath Salts (MDPV) for Scheduling Purposes

4.2.1 International Requirements and Trends in Control and/or Scheduling

Currently, there are no international controls on MDPV as MDPV is not listed on the Yellow List- List of Narcotic Drugs under International control nor the Green List-List of Psychotropic Substances under International Control.

On Oct 21 2011, as reported in the Federal Register, the U.S. Drug Enforcement Administration (DEA) a final order to temporarily schedule three synthetic cathinones and their salts, isomers and salts of isomers under the *U.S. Controlled Substances Act* (CSA) pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h) came into effect. The substances were mephedrone, methylone and MDPV. This action was based on the finding that placement of these substances on Schedule I of the CSA is necessary to avoid an imminent hazard to public safety. As a result of this order, the full effect of the CSA and its implementing regulations including criminal, civil and administrative penalties, sanctions and regulatory controls of Schedule I substances will be imposed on the manufacture, distribution, possession, importation, and exportation of these synthetic cathinones (US 2011).

Under some State laws controls have been adopted for 3,4-methylenedioxypropylone (MDPV). For instance, it is banned in the States of Louisiana, Florida and New Jersey. In the State of Kentucky it is a controlled substance and in the States of Tennessee, Maine and Ohio various controls on sale, possession and penalties have been adopted.

MDPV is also believed to be controlled abroad in Australia, the United Kingdom, Denmark, Sweden and Ireland (Drugs Forum).

In Western Australia, it is banned under the Poison Control Act of 1984. The intention to sell or supply MDPV comes with a maximum fine of \$100,000 or a 25 year imprisonment and anyone caught in possession is liable to a \$2000 fine or 2 years in jail.

In the United Kingdom, MDPV is a Class B drug under the Misuse of Drugs Act of 1971 so it is illegal to sell or possess MDPV without a license as cathinone-like psychoactive drugs are otherwise banned.

In Denmark, as of 2008, MDPV is treated as a Schedule B narcotic while in Sweden, as of 2010, MDPV is also considered a scheduled drug. In Ireland, it is controlled under the Criminal Justice Psychoactive Substances Act as of August 23, 2010.

4.2.2 Chemical and/or Pharmacological Similarity to Substances Listed in the Schedules to the CDSA

MDPV belongs to a group of substances called phenylethylamines, which are β -ketone analogs of other drugs of abuse, such as amphetamines and 3,4-methylenedioxymethamphetamine (MDMA) (J. Mugele et al., 2012).

MDPV is a synthetic stimulant related to the designer stimulant mephedrone. MDPV also shares some chemical structural features with some other CDSA scheduled substances including phenmetrazine and pyrovalerone. A Health Canada status decision as to whether or not MDPV is or is not a controlled substance recommended that MDPV is currently not a controlled substance as the listings of phenmetrazine and pyrovalerone on the schedules to the CDSA are not extended by phrases that would include MDPV.

MDPV like other controlled substances are liver metabolized by oxidation, sulfonation and conjugation reactions to effect breakdown and bodily removal by urination or excretion. MDPV shares clinical similarities to amphetamines and MDMA based on the chemical structures of these class of agents. More research is needed to understand the mechanisms of action, toxicokinetics, toxicodynamics, metabolism, clinical and psychological effects as well as the potential for addiction and withdrawal of these agents (Prosser and Nelson, 2012).

4.2.3 Legitimate Use, Including Therapeutic, Scientific, Industrial and Commercial Uses

There currently exist no legitimate therapeutic, scientific, industrial or commercial uses of “bath salts” or MDPV in Canada.

4.2.4 Potential for Abuse and/or Addiction Liability

There exists strong abuse and addiction liability potential associated with “bath salts” as indicated from past users experiences. It is often reported that when abuse is stopped that drug users experience strong cravings, suicidal tendencies and sometimes self-mutilate themselves that sometimes have resulted in death due to being overwhelmed by the psychoactive power of the drug product.

4.2.5 Evidence of Actual Abuse of the Substance in Canada and Internationally

Abuse in Canada is thought to be low and slowly rising.

Abuse in the U.S. is now thought to be widespread.

MDPV abuse has become popular in Hungary and as a consequence of its low street price, its consumption has risen so fast that the event can be considered an epidemic.

It is believed that MDPV abuse in European countries has increased dramatically these past couple of years.

4.2.6 Risk to Personal and Public Health and Safety

Although the rate of incidence of abuse and trafficking into Canada appears low and slowly rising, the severity and magnitude of the adverse effects associated with abuse and addiction of these products pose serious personal and public health and safety risks.

5. ASSESSMENT OF RISKS AND BENEFITS

There are no benefits associated with “bath salts” or MDPV.

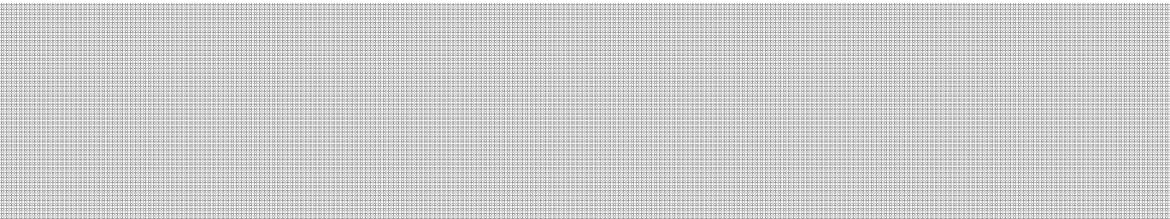
There are only serious risks to personal and public health, safety and security.

6. IDENTIFICATION AND ANALYSIS OF OPTIONS

The only option is to add MDPV, its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA.

7. CONSULTATIONS

A notice of intent (NOI) will be published in *Canada Gazette* Part I to communicate the Department’s intention to add MDPV, its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA.

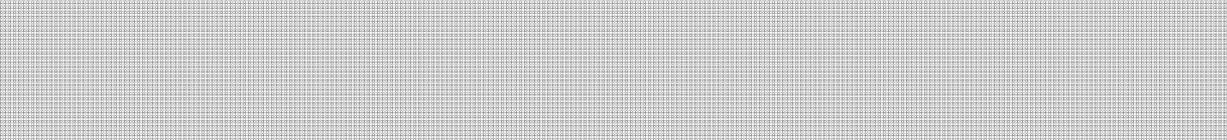


8. CONSIDERATIONS

If MDPV, its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues were not to be added to Schedule IV to the CDSA then activities of possession, sale, handling, importation and exportation of MDPV and MDPV related products would not be controlled and these dangerous abusive and addictive drugs and products would become increasingly more available in Canada for misuse and abuse.

If MDPV, its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues were to be added to Schedule IV to the CDSA then the above mentioned activities would be controlled and the related penalties for designated drug and criminal offences of the CDSA and criminal code would apply for any person found guilty of such offences. Canadian law enforcement, peace officer, border patrol officers will also be allowed to take necessary compliance and enforcement actions against illicit activity related to MDPV and products that contain MDPV to prevent further abuse, diversion and trafficking within and into Canada.

9. RECOMMENDATION



10. IMPLEMENTATION AND EVALUATION

A regulatory package will be prepared in accordance with the Cabinet Directive on Streamlining Regulation to add 3,4-methylenedioxypropylone its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA.

REFERENCES

Borek HA. Holstege CP. 2012. Hyperthermia and multiorgan failure after abuse of “bath salts” containing 3,4-methylenedioxypropylone. *Ann. Emerg. Med.* March 2

MDPV Drugs Forum. <http://www.drugs-forum.com/forum/index.php> <accessed March 9 2012>

Kyle PB. Iverson RB. Gajagowni RG. Spencer L. 2011. Illicit bath salts: not for bathing. *J. Miss. State Med. Assoc.* 52(12): 375-377.

Mugele J. Nañagas KA. Tormoehlen LM. 2012. Serotonin syndrome associated with MDPV use: a case report. *Ann. Emerg. Med.* Jan 9th.

Murray BL. Murphy CM. Beuhler MC. 2012. Death following recreational use of designer drug “bath salts” containing 3,4-methylenedioxypropylone (MDPV). *J. Med. Toxicol.* 8(1): 69-75.

Prosser JM. Nelson LS. 2012. The toxicology of bath salts: a review of synthetic cathinones. *J. Med. Toxicol.* 8(1): 33-42.

United States (DEA and Dept. of Justice). 2011. *Federal Register* October 21 2011. 76(204): 65371-5

76



Fw: MDPV
Nathan Isotalo to: Tara Phillips

2012-03-09 01:47 PM

Hi Tara,

fyi- In this regard, I believe that MDPV will need to also be added to a set of regulations.

As it does not belong on the NCR, I believe that it belongs on Part G of the FDR like phenmetrazine and pyrovalerone however, I want to double check with Hong on this point though before including it in the draft.

I will get back to you on this point.

Nathan.

----- Forwarded by Nathan Isotalo/HC-SC/GC/CA on 2012-03-09 01:42 PM -----

From: Nathan Isotalo/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-03-09 01:21 PM
Subject: Re: MDPV

Hi Tara,

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Nathan.



~~Draft Bath Salt (MDPV) Scheduling IAS Mar 9 2012.doc~~

Tara Phillips

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Date: 2012-03-08 11:24 AM
Subject: Can you pls come see me about bath salts when you have a minute?

77



re: MDPV
Nathan Isotalo to: Tara Phillips

2012-03-09 02:09 PM

Hi Tara

fyi- I checked with Hong. It needs to go on Part J as there is no therapeutic use for MDPV. I am recommending it go as sub item 1(19) as it is an analogue of amphetamine.

Nathan.



Draft Bath Salt (MDPV) Scheduling IAS Mar 9 2012v2.doc

Issue Analysis Summary

Regulation of 3,4-methylenedioxypropylamphetamine (MDPV)

Regulatory Policy Division

Office of Controlled Substances

Controlled Substances and Tobacco Directorate

March 9, 2012

CONTENTS

1. APPROVALS
2. ISSUE
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4. CONTEXT
5. ASSESSMENT OF RISKS AND BENEFITS
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DRAFT

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Johanne Beaulieu, Director
Office of Controlled Substances
Controlled Substances and Tobacco Directorate

[DD/MM/YYYY]

2. ISSUE

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Laboratory analysis has shown that these products may contain either mephedrone and/or 3,4-methylenedioxypyrovalerone (MDPV) and are often labeled as, “not for human consumption.” These products are abused for their stimulant effects from swallowing, smoking, snorting, rectal administration or the injection of them.

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Mephedrone or 4-methylmethcathinone was identified by a Health Canada status decision as an analogue of cathinone, a Schedule III listed controlled substance under the *Controlled Drugs and Substances Act* (CDSA). Cathinone is a naturally occurring β -ketone amphetamine analogue found in the leaves of the *Catha edulis* plant. Synthetic cathinones like mephedrone are derivatives of this compound.

This assessment relates to the scheduling of MDPV.

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To assess MDPV against the criteria for the addition of a substance to one of the Schedules to the CDSA, and thus determine whether it should be regulated as a controlled substance in Canada. This objective aligns with the Government of Canada's objective of restricting access to substances which may cause harm to individuals or society when diverted or misused.

4. CONTEXT

4.1 Legislative Frameworks

As "bath salts" in this case are not traditional epsom salt (magnesium sulphate) bath salt consumer products that fall under the definition of consumer product of the *Consumer Product Safety Act* (CPSA) but are new designer drug products that look like epsom salts however have a very different composition. They may contain the controlled substances, mephedrone and methylone and therefore such products are illegal in Canada as they fall under the legislative mandate of the CDSA.

4.1.1 Controlled Drugs and Substances Act and its Regulations

The CDSA provides a legislative framework for the control of substances that can alter mental processes and may produce harm to the health of an individual or to society when diverted or misused. Except as authorized under regulation, activities such as possession, trafficking, importation, exportation, possession for the purpose of trafficking or exportation, and the production of controlled substances are prohibited under the CDSA.

The CDSA and its regulations seek to support access to controlled substances for medical and scientific purposes while minimizing their diversion for illicit purposes. Controlled substances are captured under Schedule I to V of the CDSA. Drug offence contraventions under the CDSA carry penalties of varying severity described in Part I of the CDSA. Offences associated with Schedule IV are similar to those associated with substances in Schedule I, II and III except that there is no offence for simple possession.

When a substance is being considered for addition to one of the Schedules to the CDSA by the Office of Controlled Substances, Controlled Substances and Tobacco Directorate, Healthy Environments and Consumer Safety Branch, Health Canada, several factors are assessed, as follows:

- International requirements and trends in control and/or scheduling;
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- Legitimate use of the substance, including therapeutic, scientific, industrial and commercial uses;
- Potential for abuse and/or addiction liability;
- Evidence of extent of actual abuse in Canada and internationally; and,
- Risk to personal and public health and safety.

4.1.2 Food and Drugs Act and its Regulations

The *Food and Drug Regulations* (FDR) serve to ensure the safety, efficacy and quality of health products offered for sale in Canada, including drugs and medical devices. A “drug” is defined under the FDR as any substance or mixture of substances manufactured, sold or represented for use in:

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals

(b) the restoration, correction or modification of organic functions in human beings or animals, or

(c) the disinfection in premises in which food is manufactured, prepared or kept.

A substance may be added to Part G of the FDR if it has a therapeutic or medicinal use as a controlled drug whereas, it a substance may be added to Part J of the FDR if it has no therapeutic or medicinal use.

4.2 Assessment of Bath Salts (MDPV) for Scheduling Purposes

4.2.1 International Requirements and Trends in Control and/or Scheduling

Currently, there are no international controls on MDPV as MDPV is not listed on the Yellow List- List of Narcotic Drugs under International control nor the Green List-List of Psychotropic Substances under International Control.

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5. ASSESSMENT OF RISKS AND BENEFITS

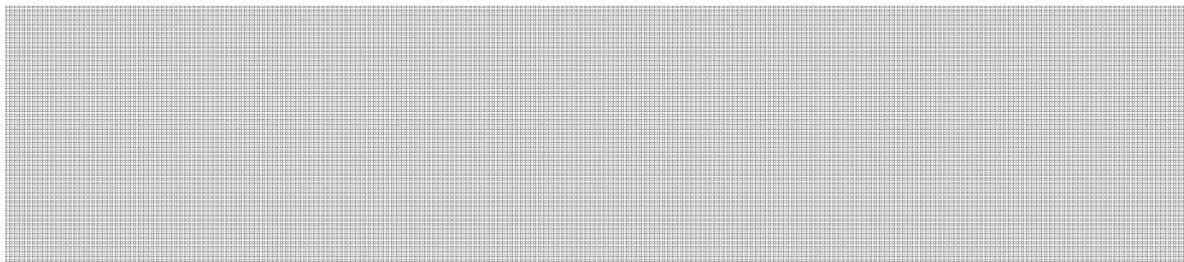
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7. CONSULTATIONS

A notice of intent (NOI) will be published in *Canada Gazette* Part I to communicate the Department’s intention to add MDPV, its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and MDPV as sub item 1(19) to Part J to the FDR.



8. CONSIDERATIONS

If MDPV, its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues were not to be added to Schedule IV to the CDSA and MDPV as sub item 1(19) to Part J to the FDR then activities of possession, sale, handling, importation and exportation of MDPV and MDPV related products would not be controlled and these dangerous abusive and addictive drugs and products would become increasingly more available in Canada for misuse and abuse.

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9. RECOMMENDATION

10. IMPLEMENTATION AND EVALUATION

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REFERENCES

Borek HA. Holstege CP. 2012. Hyperthermia and multiorgan failure after abuse of "bath salts" containing 3,4-methylenedioxypropylone. *Ann. Emerg. Med.* March 2

MDPV Drugs Forum. <http://www.drugs-forum.com/forum/index.php> <accessed March 9 2012>

Kyle PB. Iverson RB. Gajagowni RG. Spencer L. 2011. Illicit bath salts: not for bathing. *J. Miss. State Med. Assoc.* 52(12): 375-377.

Mugele J. Nañagas KA. Tormochlen LM. 2012. Serotonin syndrome associated with MDPV use: a case report. *Ann. Emerg. Med.* Jan 9th.

Murray BL. Murphy CM. Beuhler MC. 2012. Death following recreational use of designer drug "bath salts" containing 3,4-methylenedioxypropylamphetamine (MDPV). *J. Med. Toxicol.* 8(1): 69-75.

Prosser JM. Nelson LS. 2012. The toxicology of bath salts: a review of synthetic cathinones. *J. Med. Toxicol.* 8(1): 33-42.

United States (DEA and Dept. of Justice). 2011. Federal Register October 21 2011. 76(204): 65371-5

WORKPLAN: Scheduling of MDPV under the *Controlled Drugs and Substances Act*

Task/Activity		Target Date	Lead	Status
ISSUE ANALYSIS SUMMARY				
1	Research & Analysis	August 2012	RPD & ORS	Ongoing (target date for completion to be confirmed by ORS)
2	Draft Issue Analysis Summary	September 2012	RPD	
3	Controlled Substances Scheduling Working Group	September 2012	RPD & CSSWG	
4	Obtain Director, OCS approval of Issue Analysis Summary	October 2012	RPD, DO	
5	Brief senior management on Issue Analysis Summary and Workplan	October 2012	RPD	
REGULATORY PROPOSAL				
I. Notice to Interested Parties (for publication in <i>Canada Gazette</i>, Part I)				
1	Draft Notice	October 2012	RPD	
2	Consult with Treasury Board Secretariat	October 2012	RPD	
3	Obtain Director approval of Notice	November 2012	RPD, DO	
4	Obtain DG, CSTD approval of Notice	November 2012	RPD, DGO	
5	Publication in <i>Canada Gazette</i> , Part I	November 2012	RPD, DGO	
6	30-day comment period ends	December 2012	RPD, DGO	
II. Regulatory Proposal Triage				

000480

Task/Activity		Target Date	Lead	Status
1	Draft triage statement	December 2012	RPD	
2	Consult with Treasury Board Secretariat	December 2012	RPD	
3	Obtain Director approval of triage statement	January 2013	RPD, DO	
4	Obtain TBS approval of triage statement	January 2013	RPD, DGO	
III. Cost-Benefit Analysis				
1	Research & Analysis	December 2012	RPD	
2	Draft Cost-Benefit Analysis	January 2013	LSU	
IV. Preparation of Drafting Instructions				
1	Prepare drafting instructions	December 2012	RPD	
2	Legal Services Review of drafting instructions	December 2012	LSU	
3	Translate drafting instructions	December 2012	RPD	
4	Obtain Director, OCS approval of drafting instructions	January 2013	RPD, DO	
5	Obtain DG, CSTD approval of drafting instructions	January 2013	RPD, DGO	
6	Submit drafting instructions to Department of Justice Drafting Service	January 2013	RPD	

s.21(1)(a)
s.21(1)(b)
000481

Page(s) 000482 to\à 000483

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21(1)(a), 21(1)(b)

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de la Loi sur l'accès à l'information**



Revised Workplan for Scheduling MDPV
Tara Phillips to: Nathan Isotalo

2012-03-19 11:29 AM

History: This message has been replied to.

Hi Nathan,

As you can see below, Jocelyn requested a significant acceleration of the workplan. I would like to submit this to her by noon. If you have time in the next half an hour to look it over, that would be great. Please advise if you have comments.

Thank you,

Tara



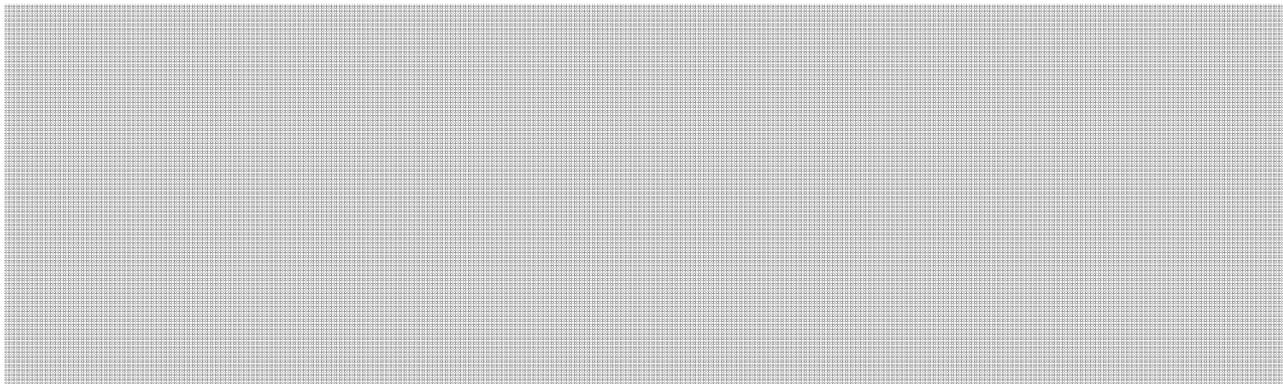
DRAFT MDPV WorkPlan Mar 19, 2012.doc

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

---- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-03-19 11:27 AM ----

From: Jocelyn Kula/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-03-19 01:09 AM
Subject: Re: For Your Review: Draft Workplan for Scheduling MDPV

s.21(1)(a)
s.21(1)(b)



Happy to discuss if needed.

JK

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224

Tara Phillips

Hi Jocelyn, Please find attached for your review...

2012-03-16 11:35:34 PM

From: Tara Phillips/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Cc: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-03-16 11:35 PM
Subject: For Your Review: Draft Workplan for Scheduling MDPV

Hi Jocelyn,

Please find attached for your review a draft workplan for scheduling MDPV.

[attachment "DRAFT MDPV WorkPlan Mar 16, 2012.doc" deleted by Jocelyn Kula/HC-SC/GC/CA]

Thank you,

Tara

WORKPLAN: Scheduling of MDPV under the Controlled Drugs and Substances Act

Task/Activity		Target Date	Lead	Status
ISSUE ANALYSIS SUMMARY				
1	Research & Analysis	March 2012	RPD & ORS	Ongoing (target date TBC by ORS)
2	Draft Issue Analysis Summary	April 2012	RPD	Ongoing
3	Controlled Substances Scheduling Working Group	April 2012	RPD & CSSWG	
4	Obtain Director, OCS approval of Issue Analysis Summary	April 2012	RPD, DO	
5	Brief senior management on Issue Analysis Summary and Workplan	April 2012	RPD	
REGULATORY PROPOSAL				
I. Regulatory Proposal Triage				
1	Draft triage statement	April 2012	RPD	
2	Consult with Treasury Board Secretariat - including One-for-One Rule (cost calculator)	April 2012	RPD	
3	Obtain Director approval of triage statement	May 2013	RPD, DO	
4	Obtain TBS approval of triage statement	May 2013	RPD, DGO	
II. Notice to Interested Parties (for publication in Canada Gazette, Part I)				
1	Draft Notice	April 2012	RPD	
2	Consult with Treasury Board Secretariat	April 2012	RPD	

	Task/Activity	Target Date	Lead	Status
3	Obtain Director approval of Notice	May 2012	RPD, DO	
4	Obtain DG, CSTD approval of Notice	May 2012	RPD, DGO	
5	Submission to Canada Gazette Directorate (6 working days in advance of publication date)	May 4, 2012	RPD, Canada Gazette Directorate	
5	Publication in <i>Canada Gazette</i> , Part I	May 12, 2012	Canada Gazette Directorate	
6	30-day comment period ends	June 11, 2012	RPD	
7	Review and analysis of comments received	June 2012	RPD	
III. Cost-Benefit Analysis				
1	Research & Analysis	May 2012	RPD	
2	Draft Cost-Benefit Analysis	May 2012	RPD	
IV. Preparation of Drafting Instructions				
1	Prepare drafting instructions	June 2012	RPD	
2	Legal Services Review of drafting instructions	June 2012	LSU	
3	Translate drafting instructions	June 2012	RPD	
4	Obtain Director, OCS approval of drafting instructions	June 2012	RPD, DO	
5	Obtain DG, CSTD approval of drafting instructions	June 2012	RPD, DGO	
6	Submit drafting instructions to Department of Justice Drafting Service	June 2012	RPD	

Page(s) 000488 to\à 000489

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21(1)(a), 21(1)(b)

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82



For Your Review: REVISED Draft Workplan for Scheduling MDPV

Tara Phillips to: Jocelyn Kula

2012-03-19 12:02 PM

Cc: Nathan Isotalo

Hi Jocelyn,

I have revised the workplan, based on your comments below. It is attached here, for your review.



DRAFT MDPV WorkPlan Mar 19, 2012.doc

With respect to your third comment, in the revised version I gave us until May rather than April to have the triage signed only because I note that the actual signing of the hardcopies adds some time (about a month in the case of tapentadol - we just received it by courier this morning). We can still have everything we need out of discussions with TBS about the triage statement prior to the end of April, which I hope addresses your point about needing information sooner.

Thank you,

Tara

Jocelyn Kula

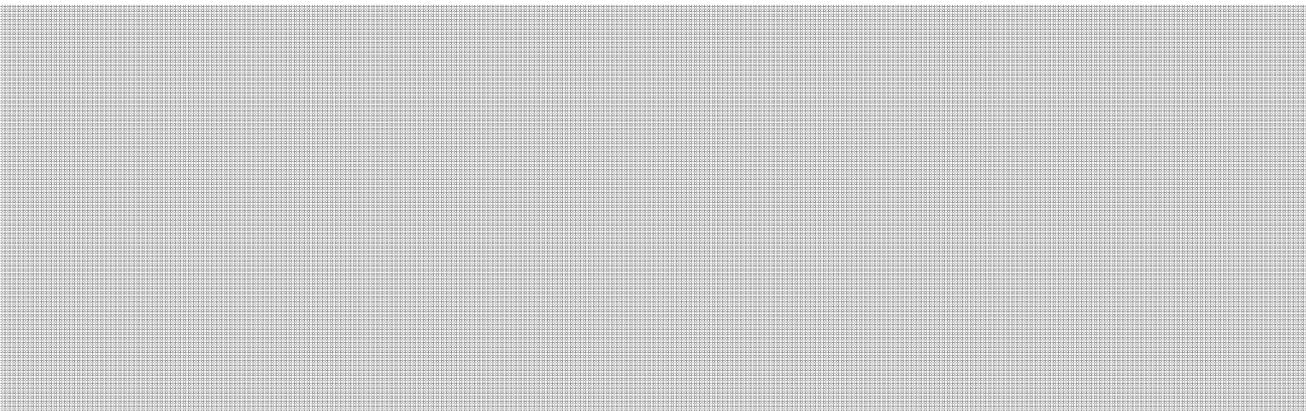
I am concerned about the length of time to do th...

2012-03-19 01:09:43 AM

From: Jocelyn Kula/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-03-19 01:09 AM
Subject: Re: For Your Review: Draft Workplan for Scheduling MDPV

s.21(1)(a)

s.21(1)(b)



Happy to discuss if needed.

JK

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire

Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs

84



Next Steps: MDPV Triage Statement
Tara Phillips to: Nathan Isotalo

2012-03-19 10:14 PM

History: This message has been replied to.

Hi Nathan,

~~Jocelyn came to see me further to the MDPV workplan I had submitted earlier today and asked that we get started on the triage statement.~~

Could you please create a draft triage statement and send to me for review by COB this Thursday, March 22nd? If you have competing priorities that could make this deadline problematic, I am always happy to discuss.

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca



re: MDPV triage
Nathan Isotalo to: Tara Phillips

2012-03-20 03:57 PM

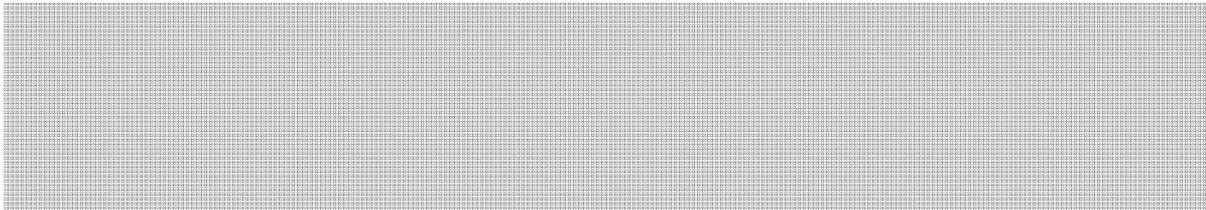


Good afternoon, Tara;

please find attached a copy of the draft triage for MDPV.



MDPV Triage 2012-03-20.rtf



s.21(1)(a)
s.21(1)(b)

For your convenience, I have placed a copy of the above at the following path:

L:\OCS\RPD\Regulatory\Projects\Scheduling\MDPV\Triage

Should you have any questions or comments please let me know.

Thank you. Nathan.

Nathan Isotalo
Sr. Policy Analyst, Regulatory Policy Division
Office of Controlled Substances
Controlled Substances and Tobacco Directorate
HECSB, Health Canada
tel. 613-941-1511



26

Triage Statement Form

s.21(1)(a)
s.21(1)(b)

Section I: Overview

Security classification
Protected B

Date received by RAS: May 2012

Title of the Regulatory Proposal: Regulation of MDPV

Sponsoring Regulatory Organization: Health Canada

Statutory Authority: *Controlled Drugs and Substances Act*

Approximate date of submission of regulatory proposal to PCO-OIC: [REDACTED]

Issue

Over the past couple of years, in North America, abuse of a new designer drug “bath salts” has steadily been increasing. These synthetic products are abused for their stimulant like effects. Substance abuse and police/border seizures of Internet marketed products known as “bath salts” has risen sharply in the United States the past few years and is slowly on the rise in Canada however, does not yet point to widespread use of “bath salt” products in the general population. These synthetic “bath salts”

Canadian Service Border Agency (CBSA) Laboratory has seen an increase in the amount of MDPV being samples for analysis. Between January 2010 and April 2011 about 16 samples had tested positive for MPDV while between April 2011 and March 2012, 24 samples had tested positive. Two of these samples were taken from two seizures of 10 barrels each of 185 kg pure MDPV.

These synthetic “bath salts” are not traditional epsom salt (hydrated magnesium sulphate) consumer products used for bathing relaxation which fall under the definition of consumer product of the *Consumer Product Safety Act* (CPSA) but are new designer drug products that may look like epsom salts however, they have a very different composition. These synthetic products may contain either mephedrone, methylone and/or 3,4-methylenedioxypropylone (MDPV) and may be sold over the Internet or in drug paraphernalia head shops in small package sizes and labelled as “bath salts” or “plant food” and “not for human consumption” in order for them to appear legal. There currently exist no legitimate therapeutic, scientific, industrial or commercial uses for these synthetic “bath salt” products or MDPV in Canada.

In Canada, both mephedrone and methylone are considered controlled substances under the *Controlled Drugs and Substances Act* (CDSA) as they are synthetic analogs of the naturally occurring β -ketone amphetamine analogue of the *Catha edulis* plant, cathinone, which is a Schedule III listed controlled substance.

MDPV belongs to a group of substances called phenylethyamines which are β -ketone analogs of amphetamines and 3,4-methylenedioxymethamphetamine (MDMA). Despite MDPV's chemical similarities to the amphetamine cathinone and other controlled substances such as phenmetrazine and pyrovalerone, currently MDPV is not considered to be scheduled under the CDSA.

These products may be abused by ingestion, snorting, injection or rectal administration. Reported adverse effects of abused bath salt products may include: hypertension, paranoia, delusions, hallucinations, tachycardia, serotonin syndrome, insomnia, psychosis, suicidal thoughts, and self-harmful tendencies such as self-mutilation and in some cases death. It is often reported that when abuse is stopped that drug users experience intense cravings a result of their physical dependence on the drug and during use tolerance thresholds are often exceeded so that more drug is needed to create the stimulant "high".

As there exist significant risks to both personal and public safety and security from the serious abuse, addiction liability and adverse effects associated with MDPV, a *Notice to Interested Parties* on the regulatory proposal will be published in *Canada Gazette* to indicate Health Canada's intent to add 3,4-methylenedioxyprovalerone (MDPV) its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and as item 1(19) to the Schedule to Part J to the *Food and Drugs Regulations* (FDR) under the *Food and Drugs Act* (FDA).

Objectives

To add 3,4-methylenedioxyprovalerone (MDPV) its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and as item 1(19) to the Schedule to Part J to the FDR. Such action would prohibit all activities, e.g., possession, importation, and exportation, involving MDPV its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues or any related products unless authorized under the NCR or a Ministerial exemption as per section 56 of the CDSA.

Description

Health Canada is proposing that 3,4-methylenedioxyprovalerone (MDPV) its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues be added to Schedule IV to the CDSA and as item 1(19) to the Schedule to Part J to the FDR.

The logo for the Government of Canada, featuring the word "Canada" in a stylized serif font with a small crown above the letter 'a'.

Page(s) 000495 to\à 000500

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Departmental signoff (*Director*): _____

Date _____

s.21(1)(a)
s.21(1)(b)

Johanne Beaulieu
Director, Office of Controlled Substances
Controlled Substances and Tobacco Directorate, HECS Branch, Health Canada

Name and address of departmental contact person:

Nathan Isotalo
123 Slater St., A304
Ottawa, ON K1A 0K9
Tel. (613) 941-1511

RAS signoff (*analyst*): _____

Date: _____

The regulatory organization should send two signed copies of the final Triage Statement to RAS. RAS will then sign the two Triage Statements and return one copy to the regulatory organization.

Regulatory Affairs Sector
Treasury Board of Canada Secretariat
155 Queen Street
Ottawa ON
K1A 0R5
Canada

87



For Your Review: Revised Workplan for Scheduling MDPV

Tara Phillips to: Jocelyn Kula

2012-03-22 01:15 PM

Cc: Nathan Isotalo

History: This message has been replied to.

Hi Jocelyn,

Please find attached, for your review, a revised MDPV workplan based on your comments and ORS' expectation that they can complete (by contract) their part of the assessment by the end of April 2012.



DRAFT MDPV WorkPlan Mar 22, 2012.doc

Thank you,

Tara

WORKPLAN: Scheduling of MDPV under the Controlled Drugs and Substances Act

Task/Activity		Target Date	Lead	Status
TRIAGE STATEMENT				
1	Draft triage statement	March 30, 2012	RPD	
2	Consult with Treasury Board Secretariat	April 13, 2012	RPD, TBS	
3	Obtain Director approval of triage statement	April 20, 2012	RPD, DO	
4	Obtain TBS approval of triage statement	April 27, 2012	RPD, DGO	
NOTICE TO INTERESTED PARTIES (Notice) - for publication in <i>Canada Gazette, Part I</i>				
1	Draft Notice	April 5, 2012	RPD	
2	Obtain Director approval of Notice	April 13, 2012	RPD, DO	
3	Obtain DG, CSTD approval of Notice	April 18, 2012	RPD, DGO	
4	Brief senior management (ADM/DM) on Notice, as required	April 25, 2012	RPD, DGO, ADMO	
5	Submission to Canada Gazette Directorate (6 working days in advance of publication date)	April 27, 2012	RPD, Canada Gazette Directorate	
6	Publication in <i>Canada Gazette, Part I</i>	May 5, 2012	Canada Gazette Directorate	
7	60-day comment period ends (Duration of comment period to be confirmed – 30, 60 or 75 days)	July 4, 2012	RPD	
8	Review and analysis of comments received	July 13, 2012	RPD	

ISSUE ANALYSIS SUMMARY				
1	Research & Analysis	May 11, 2012	RPD & ORS	Ongoing (target date TBC by ORS)
2	Draft Issue Analysis Summary	May 25, 2012	RPD	Ongoing
3	Controlled Substances Scheduling Working Group	June Meeting	RPD & CSSWG	
4	Obtain Director, OCS approval of Issue Analysis Summary	July 6, 2012	RPD, DO	
REGULATORY PROPOSAL				
I. Regulatory Cost Calculator				
1	Research & Analysis (incorporating comments received during comment period following Notice)	July 20, 2012	RPD	
2	Draft Report (cost-calculator results)	July 27, 2012	RPD	
3	Consult with Treasury Board Secretariat	August 10, 2012	RPD, TBS	
II. Preparation of Drafting Instructions				
1	Prepare drafting instructions	June 29, 2012	RPD	
2	Legal Services Review of drafting instructions	July 11, 2012	LSU	
3	Translate drafting instructions	July 13, 2012	RPD	
4	Obtain Director, OCS approval of drafting instructions	July 20, 2012	RPD, DO	
5	Obtain DG, CSTD approval of drafting instructions	July 25, 2012	RPD, DGO	

Page(s) 000506 to\à 000506

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**Work Plan for MDPV**

Jocelyn Kula to: Johanne Beaulieu
Cc: Tara Phillips, Nathan Isotalo

2012-03-22 03:15 PM

Hi Johanne

As requested, please find attached our proposed workplan for the scheduling of MDPV. Please note that we have included input from ORS as they will be undertaking the assessment of pharmacology (abuse potential, actual abuse and addiction liability) for us. Also, we have included a 60-day comment period for the NOI as we feel that this is reasonable in terms of giving stakeholders an appropriate time in which to submit comments. Lastly, we are still in discussions with TBS as to whether we will in fact have to complete the regulatory cost calculator or not, so that part of the workplan may change.



DRAFT MDPV WorkPlan Mar 22, 2012.doc

As I am away until next Tuesday, please feel free to discuss further with Tara.

Jocelyn

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire

Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et
de la sécurité des consommateurs

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Tel: (613) 946-0125 Fax: (613) 946-4224

91

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Original Article

Neuropsychopharmacology 37, 1192-1203 (April 2012) | doi:10.1038/npp.2011.304

The Designer Methcathinone Analogs, Mephedrone and Methylone, are Substrates for Monoamine Transporters in Brain Tissue

Michael H Baumann, Mario A Ayestas, John S Partilla, Jacqueline R Sink, Alexander T Shulgin, Paul F Daley, Simon D Brandt, Richard B Rothman, Arnold E Ruoho and Nicholas V Cozzi

The nonmedical use of 'designer' cathinone analogs, such as 4-methylmethcathinone (mephedrone) and 3,4-methylenedioxymethcathinone (methylone), is increasing worldwide, yet little information is available regarding the mechanism of action for these drugs. Here, we employed in vitro and in vivo methods to compare neurobiological effects of mephedrone and methylone with those produced by the structurally related compounds, 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine. In vitro release assays using rat brain synaptosomes revealed that mephedrone and methylone are nonselective substrates for plasma membrane monoamine transporters, similar to MDMA in potency and selectivity. In vivo microdialysis in rat nucleus accumbens showed that i.v. administration of 0.3 and 1.0 mg/kg of mephedrone or methylone produces dose-related increases in extracellular dopamine and serotonin (5-

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- ▶ Alexander T Shulgin
- ▶ Paul F Daley
- ▶ more authors of this article

HT), with the magnitude of effect on 5-HT being greater. Both methcathinone analogs were weak motor stimulants when compared with methamphetamine. Repeated administrations of mephedrone or methylone (3.0 and 10.0 mg/kg, s.c., 3 doses) caused hyperthermia but no long-term change in cortical or striatal amines, whereas similar treatment with MDMA (2.5 and 7.5 mg/kg, s.c., 3 doses) evoked robust hyperthermia and persistent depletion of cortical and striatal 5-HT.

partner of AGORA, HINARI, OARE, INASP, ORCID, CrossRef and COUNTER

Our data demonstrate that designer methcathinone analogs are substrates for monoamine transporters, with a profile of transmitter-releasing activity comparable to MDMA. Dopaminergic effects of mephedrone and methylone may contribute to their addictive potential, but this hypothesis awaits confirmation. Given the widespread use of mephedrone and methylone, determining the consequences of repeated drug exposure warrants further study.

To read this article in full you may need to log in, make a payment or gain access through a site license (see right).

Neuropsychopharmacology ISSN 0893-133X EISSN 1470-634X

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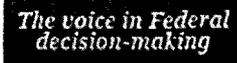
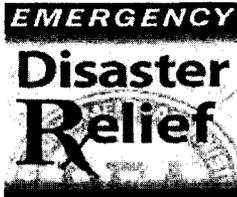
Federal Register Notices > Rules - 2011 > Temporary Placement of Three Synthetic Cathinones Into Schedule I

Information and Legal Resources at your fingertips

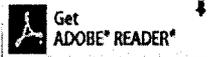


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[Federal Register Volume 76, Number 204 (Friday, October 21, 2011)]
[Rules and Regulations]
[Pages 65371-65375]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2011-27282]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-357]

Schedules of Controlled Substances: Temporary Placement of Three Synthetic Cathinones Into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final Order.

SUMMARY: The Administrator of the Drug Enforcement Administration (DEA) is issuing this final order to temporarily schedule three synthetic cathinones under the Controlled Substances Act (CSA) pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). The substances are 4-methyl-N-methylcathinone (mephedrone), 3,4-methylenedioxy-N-methylcathinone (methylone), and 3,4-methylenedioxypyrovalerone (MDPV). This action is based on a finding by the Administrator that the placement of these synthetic cathinones and their salts, isomers, and salts of isomers into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. As a result of this order, the full effect of the CSA and its implementing regulations including criminal, civil and administrative penalties, sanctions and regulatory controls of Schedule I substances will be imposed on the manufacture, distribution, possession, importation, and exportation of these synthetic cathinones.

DATES: Effective Date: [This Final Order is effective on October 21, 2011.]

FOR FURTHER INFORMATION CONTACT: Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone (202) 307-7165.

SUPPLEMENTARY INFORMATION:

Background

The Comprehensive Crime Control Act of 1984 (Pub. L. 98-473), which was signed into law on October 12, 1984, amended section 201 of the CSA (21 U.S.C. 811) to give the Attorney General the authority to temporarily place a substance into Schedule I of the CSA for one year without regard to the requirements of 21 U.S.C. 811(b) if he finds that such action is necessary to avoid imminent hazard to the public safety. 21 U.S.C. 811(h); 21 CFR 1308.49. If proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1), the Attorney General may extend the temporary scheduling up to an additional six months. 21 U.S.C. 811(h)(2). Where the necessary findings are made, a substance may be temporarily scheduled in Schedule I if it is not listed in any other schedule under section 202 of the CSA (21 U.S.C. 812) or if there is no exemption or approval in effect under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) for the substance. 21 U.S.C. 811(h)(1). The Attorney General has delegated his authority under 21 U.S.C. 811 to the Administrator of DEA. 28 CFR 0.100.

Section 201(h)(4) of the CSA (21 U.S.C. 811(h)(4)) requires the Administrator to notify the Secretary of Health and Human Services of her intention to temporarily place a substance into Schedule I of the CSA.11

[[Page 65372]]

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The Administrator transmitted notice of her intent to place mephedrone, methylone and MDPV in Schedule I on a temporary basis to the Assistant Secretary in a letter dated June 15, 2011. The Assistant Secretary responded to this notice by letter dated July 25, 2011, and advised that based on review by the Food and Drug Administration (FDA) there are currently no investigational new drug applications (INDs) or approved new drug applications (NDAs) for MDPV, mephedrone, or methylone. The Assistant Secretary also stated that the Department of Health and Human Services has no objection to the temporary placement of MDPV, mephedrone, and methylone into Schedule I of the CSA. DEA has taken into consideration the Assistant Secretary's comments. As MDPV, mephedrone, and methylone are not currently listed in any schedule under the CSA, as no exemptions or approvals are in effect for MDPV, mephedrone, and methylone under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), and as this temporary scheduling is necessary to avoid an imminent hazard to the public safety, DEA believes that the conditions of 21 U.S.C. 811(h)(1) have been satisfied.

¹¹ Because the Secretary of Health and Human Services has delegated to the Assistant Secretary for Health of the Department of Health and Human Services the authority to make domestic drug scheduling recommendations, for purposes of this Final Order, all subsequent references to "Secretary" have been replaced with "Assistant Secretary."

A notice of intent to temporarily place mephedrone, methylone, and MDPV into Schedule I of the CSA was published in the Federal Register on September 8, 2011 (76 FR 55616). The data in support of the notice of intent and additional data continue to support the necessary findings to place mephedrone, methylone, and MDPV temporarily into Schedule I of the CSA as necessary to avoid an imminent hazard to the public safety.¹² In making this finding, the Administrator is required to consider three of the eight factors set forth in section 201(c) of the CSA (21 U.S.C. 811(c)). These factors are as follows: The substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(c)(4)-(6). Consideration of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

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US notes in

¹² See "Background, Data and Analysis of Synthetic Cathinones: Mephedrone (4-MMC), Methylone (MDMC) and 3,4-Methylenedioxypyrovalerone (MDPV)" found at <http://www.regulations.gov>.

Mephedrone, methylone, and MDPV are not currently listed in any schedule under the CSA. The temporary placement of these three synthetic cathinones into Schedule I of the CSA is necessary in order to avoid an imminent hazard to the public safety. First, there has been a rapid and significant increase in abuse of these substances in the United States. As a result of this abuse, synthetic cathinones are banned in at least 37 states in the United States and several countries, and all five branches of the U.S. military prohibit military personnel from possessing or using synthetic cathinones. Second, law enforcement has seized synthetic cathinones and, based on self-reports to law enforcement and health care professionals, synthetic cathinones are abused for their psychoactive properties. Third, federal, state and local public health departments and poison control centers have issued reports describing public health consequences such as emergency department visits and deaths from the use of these synthetic cathinones. Based on scientific data currently available, these three substances have the potential to be extremely harmful and, therefore, pose an imminent hazard to the public safety.

Factor 4: History and Current Pattern of Abuse

Synthetic cathinones are designer drugs of the phenethylamine class which are structurally and pharmacologically similar to amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), cathinone and other related substances. The addition of a beta-keto (beta-keto) substituent to the phenethylamine core structure produces a group of substances that now have cathinone as the core structure. Synthetic cathinones, like amphetamine, cathinone, methcathinone, and methamphetamine, are central nervous system (CNS) stimulants.

2011, US data

The synthetic cathinones mephedrone, methylone, and MDPV have recently emerged on the United States' illicit drug market and are being perceived as being "legal" alternatives to cocaine, methamphetamine, and MDMA. Although synthetic cathinones are new to the United States' illicit drug market, they have been popular drugs of abuse in Europe since 2007. MDPV is a derivative of pyrovalerone, which is a psychoactive drug that was used to treat chronic lethargy and fatigue. Research in anti-depressant and anti-parkinson agents resulted in the development and patenting of methylone. Methylone, however, has not been approved for these purposes. There are no currently accepted medical uses in treatment in the United States for mephedrone, methylone, or MDPV.

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Mephedrone, methylone, and MDPV are falsely marketed as "research chemicals," "plant food," or "bath salts." They are sold at smoke shops, head shops, convenience stores, adult book stores, and gas stations. They can also be purchased on the Internet and mailed using the U.S. Postal Service or international mail services. The packages of products containing these synthetic cathinones usually have the warning "not for human consumption," most likely in an effort to circumvent statutory restrictions for these substances. Despite disclaimers that the products are not intended for human consumption, retailers promote that routine urinalysis drug tests will not typically detect the presence of these synthetic cathinones. However, analytical methods for the detection of mephedrone, methylone, MDPV, and other synthetic cathinones have recently been developed for these substances.

Evidence indicates that mephedrone, methylone, and MDPV are being abused for their psychoactive properties. Drug surveys found that these and other synthetic cathinones are being used as recreational drugs and are used as alternatives to illicit stimulants like MDMA and cocaine. Accordingly, mephedrone, methylone, and MDPV have been identified in human urine samples that were obtained for routine drug screenings, they have been detected in samples from drivers suspected of driving under the influence, and they have been detected by drug courts during mandatory periodic drug screens. They have also been identified in biological specimens from individuals (some exhibiting symptoms of "extreme agitation" or "excited delirium") who have been arrested for possession of a controlled substance, child endangerment,

Subs.

or homicide). They have been detected in samples from decedents whose causes of death were reported as drug-induced toxicity, multiple drug toxicity, or other causes (e.g., blunt force trauma from a vehicular collision or suicide).

Based on studies in the scientific literature, the marketing of products that contain mephedrone, methylone, and MDPV is geared towards teens and young adults. Accordingly, reports indicate that the main users of synthetic cathinones are young male adults. These substances are also used by mid-to-late adolescents and older adults. Many of these abusers of synthetic cathinones have a previous history of drug abuse.

[[Page 65373]]

abuse of Synthetic Cathinones - esp. route

According to drug surveys, the reported average amount of synthetic cathinones used per dose ranged from approximately 25 to 250 milligrams and the average amount used per session (i.e., repeated administration and binging) ranged from approximately 25 milligrams to 5 grams depending on the substance consumed, duration of intake, and route of administration. The most common routes of administration of these substances are nasal insufflation by snorting the powder and oral ingestion by swallowing capsules or tablets. Other reported methods of administration include injection, rectal administration, and "bombing" (wrapping a dose of powder in a paper wrap and swallowing). Synthetic cathinones have also been reported to be used in binges. Reasons cited for binging include to prolong the duration of effects, to satisfy a "craving," or to satisfy a strong urge to re-dose.

According to information found in drug surveys, clinical case reports, and law enforcement reports, users have reported using products containing mephedrone, methylone, and MDPV with other synthetic cathinones (e.g., butylone, fluoromethcathinone, 4-MEC, etc.), pharmaceutical agents (e.g., lidocaine, caffeine, benzocaine, etc.), or other recreational substances (e.g., amphetamine, MDMA, cocaine, gamma-butyrolactone (GBL), kratom, N,N-benzylpiperazine (BZP), and 1-(3-trifluoromethylphenyl)-piperazine (TFMPP)). Chemical analyses of seized and purchased synthetic cathinone products indicate that some products contain multiple substances. Furthermore, investigative toxicology reports of drug screens in which more than one substance was detected indicate that users have ingested products composed of drug combinations (e.g., a tablet composed of MDPV and BZP) or multiple drug products (e.g., a MDPV powder product and a MDMA tablet).

Factor 5: Scope, Duration and Significance of Abuse

The popularity of synthetic cathinones as recreational drugs has increased since they first appeared on the United States' illicit drug market. According to forensic laboratory reports, the first appearance of these synthetic cathinones in the United States occurred in 2009. In 2009, NFLIS registered 15 exhibits from 8 states containing these three synthetic cathinones. In 2010, there were 574 reports from 29 states related to these substances registered in NFLIS, and in 2011 (January to August) there were 995.¹³¹

¹³¹ Analyzed on September 15, 2011.

Based on reports to DEA from law enforcement and public health officials, synthetic cathinones are becoming increasingly prevalent and abused throughout the United States. At one United States point of entry, the U.S. Customs and Border Protection (CBP) has encountered at least 127 shipments containing primarily mephedrone, methylone, and MDPV, as well as other synthetic cathinones like 4-MEC, butylone, fluoromethcathinone, and dimethylcathinone. Most of these shipments originated in China or India and were being shipped to destinations throughout the United States such as Arizona, Alaska, Hawaii, Kansas, Louisiana, Oklahoma, Oregon, Pennsylvania, Missouri, Virginia, Washington, and West Virginia. The American Association of Poison Control Centers (AAPCC), a non-profit, national organization that represents the poison control centers of the United States, reported that in 2010, poison control centers took 303 calls about synthetic cathinones. However, in just the first eight months of 2011, poison control centers have already received 4,720 calls relating to these products. These calls were received in poison control centers representing at least 47 states and the District of Columbia. Individual state poison control centers have also reported an increase in the number of calls regarding "bath salts" from 2009 to 2011.

Emergency Schedule

Concerns over the abuse of these and other synthetic cathinones have prompted many states to control these substances. As of September 15, 2011, at least 37 states have emergency scheduled or enacted legislation placing regulatory controls on some or many of the synthetic cathinones. These states include Alabama, Arkansas, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Michigan, Minnesota, Mississippi, Missouri, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Tennessee, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin and Wyoming. Several countries including all members of the European Union have also placed controls on the possession and/or sale of one or more of these substances. Moreover, the use of synthetic cathinones by members of the U.S. Armed Forces is prohibited.

Factor 6: What, if Any, Risk There Is to the Public Health

The risks to the public health associated with the abuse of mephedrone, methylone, and MDPV relate to acute and long term public health and safety problems. These synthetic cathinones have become a serious drug abuse threat as there have been reports of emergency room admissions and deaths associated with the abuse of these substances.

Clinical case reports indicate that these synthetic cathinones produce a number of stimulant-like adverse effects such as palpitation, seizure, vomiting, sweating, headache, discoloration of the skin, hypertension, and hyper-reflexia. Adverse effects associated with consumption of these drugs as reported by abusers include nose-bleeds, bruxism (teeth grinding), paranoia, hot flashes, dilated pupils, blurred vision, dry mouth/thirst, palpitations, muscular tension in the jaw and limbs, headache, agitation, anxiety, tremor, and fever or sweating. Consequently, numerous individuals have presented at emergency departments in response to exposure incidents and several cases of acute toxicity have been reported due to the ingestion

of mephedrone, methylone, or MDPV. In addition, case reports have shown that the abuse of synthetic cathinones can lead to psychological dependence like that reported for other stimulant drugs.

According to clinical case reports, investigative toxicological reports, and autopsy reports, mephedrone, methylone, and MDPV have been implicated in drug induced overdose deaths. In at least three reported deaths, one of these synthetic cathinones was ruled as the cause of death. Other deaths involved individuals under the influence of these synthetic cathinones who acted violently and unpredictably in causing harm to themselves or others. There have also been reports in the scientific literature of deaths caused by individuals who were driving under the influence of these synthetic cathinones.

A number of synthetic cathinones and their products, as identified by CBP and reported in the scientific literature, appear to originate from foreign sources. The manufacturers and retailers who make and sell these products do not fully disclose the product ingredients including the active ingredients or the health risks and potential hazards associated with these products. This poses significant risk to abusers who may not know what they are purchasing or the risk associated with the use of those products.

[[Page 65374]]

Based on the above data, the continued uncontrolled manufacture, distribution, importation, exportation, and abuse of mephedrone, methylone, and MDPV pose an imminent hazard to the public safety. DEA is not aware of any recognized therapeutic uses of these synthetic cathinones in the United States.

DEA has considered the three criteria for placing a substance into Schedule I of the CSA (21 U.S.C. 812), and finds that the data available and reviewed for mephedrone, methylone, and MDPV indicate that these synthetic cathinones each have a high potential for abuse, no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision.

In accordance with the provisions of section 201(h) of the CSA (21 U.S.C. 811(h)) and 28 CFR 0.100, the Administrator has considered the available data and the three factors required to support a determination to temporarily schedule three synthetic cathinones (4- methyl-N-methylcathinone, 3,4-methylenedioxy-N-methylcathinone, and 3,4-methylenedioxypropylvalerone) in Schedule I of the CSA and finds that placement of these synthetic cathinones and their salts, isomers, and salts of isomers into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety.

Regulatory Requirements

With the issuance of this final order, mephedrone, methylone, and MDPV become subject to the regulatory controls and administrative, civil and criminal sanctions applicable to the manufacture, distribution, possession, importation and exportation of a Schedule I controlled substance under the CSA.

1. **Registration.** Any person who manufactures, distributes, dispenses, imports, exports, or possesses mephedrone, methylone, or MDPV or who engages in research or conducts instructional activities with respect to mephedrone, methylone, or MDPV, or who proposes to engage in such activities, must be registered to conduct such activities in accordance with 21 U.S.C. 823 and 958. Any person who is currently engaged in any of the above activities and is not registered with DEA must submit an application for registration and may not continue their activities until DEA has approved that application. Retail sales of Schedule I controlled substances to the general public are not allowed under the Controlled Substances Act.
2. **Security.** Mephedrone, methylone, and MDPV are subject to Schedule I security requirements. Accordingly, appropriately registered DEA registrants must manufacture, distribute and store these substances in accordance with 1301.71; 1301.72(a), (c), and (d); 1301.73; 1301.74; 1301.75(a) and (c); and 1301.76 of Title 21 of the Code of Federal Regulations as of October 21, 2011.
3. **Labeling and packaging.** All labeling and packaging requirements for controlled substances set forth in Part 1302 of Title 21 of the Code of Federal Regulations shall apply to commercial containers of mephedrone, methylone, and MDPV. Current DEA registrants shall have thirty (30) calendar days from the effective date of this Final Order to be in compliance with all labeling and packaging requirements.
4. **Quotas.** Quotas for mephedrone, methylone, and MDPV will be established based on registrations granted and quota applications received pursuant to Part 1303 of Title 21 of the Code of Federal Regulations.
5. **Inventory.** Every DEA registrant who possesses any quantity of mephedrone, methylone, or MDPV is required to keep inventory of all stocks of these substances on hand pursuant to 1304.03, 1304.04, and 1304.11 of Title 21 of the Code of Federal Regulations. Every current DEA registrant who desires registration in Schedule I for mephedrone, methylone, or MDPV shall conduct an inventory of all stocks of these substances. Current DEA registrants shall have thirty (30) calendar days from the effective date of this Final Order to be in compliance with all inventory requirements.
6. **Records.** All registrants who handle mephedrone, methylone, or MDPV are required to keep records pursuant to 1304.03, 1304.04, 1304.21, 1304.22, and 1304.23 of Title 21 of the Code of Federal Regulations. Current DEA registrants shall have thirty (30) calendar days from the effective date of this Final Order to be in compliance with all recordkeeping requirements.
7. **Reports.** All registrants are required to submit reports in accordance with 1304.33 of Title 21 of the Code of Federal Regulations. Registrants who manufacture or distribute mephedrone, methylone, or MDPV are required to comply with these reporting requirements and shall do so as of October 21, 2011.
8. **Order Forms.** All registrants involved in the distribution of mephedrone, methylone, or MDPV must comply with order form requirements of Part 1305 of Title 21 of the Code of Federal Regulations as of October 21, 2011.
9. **Importation and Exportation.** All importation and exportation of mephedrone, methylone, or MDPV must be conducted by appropriately registered DEA registrants in compliance with Part 1312 of Title 21 of the Code of Federal Regulations on or after October 21, 2011.

10. Criminal Liability. The manufacture, distribution, dispensation, or possession with the intent to conduct these activities: Possession, importation, or exportation of mephedrone, methylone, or MDPV not authorized by, or in violation of the CSA or the Controlled Substances Import and Export Act occurring as of October 21, 2011 is unlawful.

Pursuant to the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act) (5 U.S.C. 801-808), DEA has submitted a copy of this Final Order to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

Under the authority vested in the Attorney General by section 201(h) of the CSA (21 U.S.C. 811(h)), and delegated to the Administrator of the DEA by Department of Justice regulations (28 CFR 0.100), the Administrator hereby orders that 21 CFR Part 1308 be amended as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for Part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

- 2. Section 1308.11 is amended by adding new paragraphs (g)(6), (7) and (8) to read as follows:

Sec. 1308.11 Schedule I.

(g) ***

(6) 4-methyl-N-methylcathinone--1248
(Other names: mephedrone)

(7) 3,4-methylenedioxy-N-methylcathinone--7540
(Other names: methylone)

(8) 3,4-methylenedioxypropylvalerone--7535
(Other names: MDPV)

[[Page 65375]]

Dated: October 14, 2011.

Michele M. Leonhart,
Administrator.

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[Back to Top](#)

[Drug Enforcement Administration Home](#) 

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JPET #184119

Title Page

**4-Methylmethcathinone (Mephedrone): Neuropharmacological
Effects of a Designer Stimulant of Abuse**

Gregory C. Hadlock, Katy M. Webb, Lisa M. McFadden, Pei Wen Chu,
Jonathan D. Ellis, Scott C. Allen, David M. Andrenyak, Paula L. Vieira-Brock, Christopher L. German,
Kevin M. Conrad, Amanda J. Hoonakker, James W. Gibb, Diana G. Wilkins,
Glen R. Hanson, and Annette E. Fleckenstein

Department of Pharmacology & Toxicology, University of Utah, 30 S 2000 E, Rm. 201, Salt Lake City,
UT 84112

JPET #184119

Running Title Page

Running Title: Mephedrone and Monoaminergic Neuronal Function

Corresponding Author:

Annette E. Fleckenstein, Ph.D.

Professor

University of Utah

Department of Pharmacology & Toxicology

30 South 2000 East, Room 201

Salt Lake City, UT 84112

e-mail: fleckenstein@hsc.utah.edu

telephone: 801-585-7474

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Abbreviations:

1-(4-Methylphenyl)-2-methylaminopropane-1-one

4-methylmethcathinone, mephedrone; 1-(benzo[d][1,3]dioxol-5-yl)-N-methylpropan-2-amine,

methylenedioxymethamphetamine, MDMA; 2-(methylamino)-1-phenyl-propan-1-one, methcathinone,

MCAT; 5-hydroxytryptamine, serotonin, 5HT; dopamine, DA; N-methyl-1-phenylpropan-2-amine,

methamphetamine, METH; rotating disc electrode, RDE.

JPET #184119

Abstract

The designer stimulant, 4-methylmethcathinone (mephedrone), is among the most popular of the derivatives of the naturally occurring psychostimulant, cathinone. Mephedrone has been readily available for legal purchase both online and in some stores, and has been promoted by aggressive web-based marketing. Its abuse in many countries, including the United States, is a serious public health concern. Owing largely to its recent emergence, there are no formal pharmacodynamic or pharmacokinetic studies of mephedrone. Accordingly, the purpose of this study was to evaluate effects of this agent in a rat model. Results revealed that, similar to methylenedioxymethamphetamine, methamphetamine and methcathinone, repeated mephedrone injections (4 x 10 - 25 mg/kg/injection, s.c., 2-h intervals, administered in a pattern used frequently to mimic psychostimulant "binge" treatment) cause a rapid decrease in striatal dopamine (DA) and hippocampal serotonin (5-hydroxytryptamine; 5HT) transporter function. Mephedrone also inhibited both synaptosomal DA and 5HT uptake. Like methylenedioxymethamphetamine, but unlike methamphetamine or methcathinone, repeated mephedrone administrations also caused persistent serotonergic, but not dopaminergic, deficits. However, mephedrone caused DA release from a striatal suspension approaching that of methamphetamine, and was self-administered by rodents. A method was developed to assess mephedrone concentrations in rat brain and plasma, and mephedrone levels were determined 1 h after a "binge" treatment. These data demonstrate that mephedrone has a unique pharmacological profile with both abuse liability and neurotoxic potential.

JPET #184119

Introduction

The designer drug, 4-methylmethcathinone (mephedrone), is among the most popular of the derivatives of the naturally occurring psychostimulant, cathinone (Cressey, 2010; ACMD, 2010; Morris, 2010). Its structure is closely related to the phenylethylamine-family of illicit agents including methamphetamine (METH) and methylenedioxymethamphetamine (MDMA), differing by a keto group at the beta carbon. Mephedrone has been readily available for purchase both on- and off-line, and its circulation has been promoted by web-based marketing. Its rise in popularity in the United Kingdom received international attention, and led to its ban in 2010. Also in 2010, there were increasing reports of the abuse and seizure liability of mephedrone in regions other than Europe, including South-East Asia, Australia, and North America. Its abuse in the United States, particularly in the form of "Ivory Wave" (e.g., its combination with the stimulant, 3,4-methylenedioxypyrovalerone) has become a health concern.

Owing largely to its recent emergence, there are very few formal pharmacodynamic or pharmacokinetic studies of mephedrone. A single report by Kehr et al. (in press) indicates that mephedrone causes DA release in the nucleus accumbens. Beyond this, clinical and anecdotal reports are the primary source of information concerning mephedrone. This lack of information is problematic for public health policy makers and law enforcement organizations as they attempt to develop and implement appropriate strategies for dealing with the recreational use and abuse of mephedrone and related drugs. Of further concern, it has been suggested that mephedrone may resemble dangerous drugs such as methcathinone (MCAT), MDMA, or METH. This is problematic, as it is well established that high-dose administration of these stimulants can cause long-lasting monoaminergic deficits in humans (McCann et al., 1998; Sekine et al., 2001; Reneman et al., 2001) and non-human models (Ricaurte et al., 1980; Wagner et al., 1980; Guilarte et al., 2003; Hotchkiss et al., 1979; Sparago et al., 1996; Nash and Yamamoto, 1992; Gygi et al., 1997; Mereu et al., 1983). The potential clinical relevance of understanding these changes is underscored by findings that stimulant (e.g., METH) abusers often display general persistent impairment across several

JPET #184119

neurocognitive domains, including deficits in executive function and memory (Volkow et al., 2001; Scott et al., 2007).

As noted, there are currently very few published studies describing the pharmacological or toxicological impact of mephedrone. Thus, the present study addresses this issue. Results revealed that, similar to MDMA, METH and MCAT (Fleckenstein et al., 1999; Metzger et al., 2000; Haughey et al., 2000; Hansen et al., 2002), repeated mephedrone injections rapidly decrease dopamine (DA) and serotonin (5-hydroxytryptamine; 5HT) transporter function. Like MDMA, but unlike METH (Stone et al., 1986; Schmidt and Kehne, 1990; McCann et al., 1994; Reneman et al., 2001; Krasnova and Cadet, 2009) repeated mephedrone administrations cause persistent serotonergic, but not dopaminergic, deficits. Of note, mephedrone causes DA release from a striatal suspension approaching that of METH, and is self-administered by rodents. These data demonstrate important similarities and differences among mephedrone and other related stimulants of abuse. Moreover, these data demonstrate that mephedrone has a unique pharmacological profile with both abuse liability and neurotoxic potential.

JPET #184119

Methods

Animals. Male Sprague-Dawley rats (290-400 g; Charles River Laboratories, Raleigh, NC) were maintained under controlled lighting and temperature conditions with constant access to food and water. With the exception of rats in the self-administration experiments, which were singly housed, rats were housed 3-4 animals per cage during treatment. Rats were maintained in a warmer ambient environment during treatment (e.g., $\geq 27^{\circ}\text{C}$) to ensure that the mephedrone-treated rats attained hyperthermia. Temperatures were assessed at 1-h intervals beginning 30 min before the first saline or mephedrone injections. Rats were sacrificed by decapitation. All procedures were conducted in accordance with National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and approved by the University of Utah Institutional Animal Care and Use Committee.

Drugs and Chemicals. Mephedrone hydrochloride, METH hydrochloride, cocaine hydrochloride, and MDMA hydrochloride were supplied by the Research Triangle Institute (Research Triangle Park, NC). Fluoxetine hydrochloride, cefazolin, and heparinized saline were purchased from Sigma Aldrich (St. Louis, MO). Mephedrone- d_3 was purchased from Cerilliant (Round Rock, TX). Mephedrone, METH, cocaine, and MDMA were dissolved in 0.9% saline vehicle prior to administration. Drug doses were calculated as the free base.

Synaptosomal [^3H]DA and [^3H]5HT uptake. [^3H]DA and [^3H]5HT uptake were determined using a rat striatal (DA) or hippocampal (5HT) synaptosomal preparation as previously described (Kokoshka et al., 1998a). In brief, synaptosomes were prepared by homogenizing freshly dissected striatal or hippocampal tissue in ice-cold 0.32 M sucrose pH 7.4, and centrifuged (800 x g, 12 min; 4°C). In some experiments, small sections of the left anterior striatum and left anterior hippocampus were quickly frozen on dry ice and retained for determining DA and 5HT content. The supernatants were centrifuged (22,000 x g, 15 min; 4°C) and the resulting pellets were resuspended in ice-cold assay buffer (in mM: 126 NaCl, 4.8 KCl, 1.3 CaCl₂, 16 sodium phosphate, 1.4 MgSO₄, 11 glucose and 1 ascorbic acid; pH 7.4) and 1 μM pargyline. For the IC₅₀ experiments, cocaine, MDMA, or mephedrone

JPET #184119

(1 nM - 5 μ M) was present in the assay tubes. Samples were incubated for 10 min at 37 °C and the assays initiated by the addition of [3 H]DA or [3 H]5HT (0.5 nM or 5 nM final concentration, respectively). Following incubation for 3 min, samples were placed on ice to stop the reaction. Samples were then filtered through GF/B filters (Whatman, Florham Park, NJ) soaked previously in 0.05% polyethylenimine. Filters were rapidly washed three times with 3 ml of ice-cold 0.32M sucrose buffer using a filtering manifold (Brandel, Gaithersburg, MD). For [3 H]DA uptake, nonspecific values were determined in the presence of 50 μ M cocaine. For [3 H]5HT uptake, nonspecific values were determined in the presence of 10 μ M fluoxetine. Radioactivity trapped in filters was counted using a liquid scintillation counter. Protein concentrations were determined using the Bio-Rad Protein Assay (Bio-Rad Laboratories Inc., Hercules, CA).

DA and 5HT Concentrations. Striatal and hippocampal tissues were quickly frozen on dry ice and stored at -80°C until sonication (Branson Sonifier 250; Branson Ultrasonics Corporation, Danbury, CT) in 1 ml of tissue buffer (50 mM sodium phosphate dibasic, 30 mM citric acid with 10% (v/v) methanol, pH 2.5), then centrifuged at 18,800 x g for 15 min at 4 °C to separate the supernatant from the protein. The supernatant was centrifuged at 18,800 x g for 10 min at 4°C, and 25 μ l was injected onto a high-performance liquid chromatography system (Dynamax AI-200 Autosampler and SD-200 pump; Varian, Walnut, CA) coupled to an electrochemical detector (E_{ox} = +0.70 V; Varian Star 9080) to quantitate the concentrations of DA and 5HT. Monoamines were separated on a Whatman PartiSphere C-18 column (250 \times 4.6 mm, 5 μ m; Whatman, Clifton, NJ) in mobile phase consisting of 25% (v/v) MeOH, 0.04% (w/v) sodium octyl sulfate, 0.1 mM EDTA, 50 mM sodium phosphate dibasic, and 30 mM citric acid, at a pH of 2.65 and a flow rate of 0.75 ml/min. Protein concentrations were determined using the Bio-Rad Protein Assay (Bio-Rad Laboratories Inc., Hercules, CA).

Mephedrone Concentrations. Rat brains were homogenized separately by weighing each brain sample and homogenizing with 10 ml of MilliQ water. For the extraction, 0.5 ml of each plasma and brain homogenate was transferred to separate glass tubes. Mephedrone- d_3 (30 mg) was added as

JPET #184119

the internal standard. A 0.1 ml volume of ammonium hydroxide and 4 ml of 1-chlorobutane: acetonitrile (4:1, v:v) was added to each tube. After mixing and centrifugation, the upper organic layers were transferred to separate culture tubes and evaporated to dryness at 40 °C under air. A 0.1 ml volume of 0.2 % formic acid: methanol (75:25, v:v) was added to each extract. The reconstituted extracts were transferred to separate polypropylene autosampler vials. The extracts were analyzed on a Waters Acuity liquid chromatograph interfaced with a Waters Premier XE Quattro tandem mass spectrometer (Waters, Waltham, MA). Chromatographic conditions used a Synergi MAX RP 150 x 2 mm column (Phenomenex, Torrance, CA). The mobile phase consisted of 0.2 % formic acid: methanol (75:25, v:v) at a 0.2 ml/minute flow rate. Positive ion electrospray was used for the ionization. Selection reaction monitoring was used to monitor the peak areas for mephedrone (m/z 178→160) and mephedrone- d_3 (m/z 181→163). For both compounds, a cone voltage of 25 V and a collision energy of 15 V were utilized. Calibration standards (1 to 500 ng/ml) and quality control samples (8, 80, and 240 ng/ml) were prepared by fortification of a known concentration of drug to analyte-free matrix and were concurrently analyzed with the study samples. The study samples were diluted appropriately so that measured mephedrone concentrations were within the range of the calibration curve.

Rotating Disk Electrode (RDE) Voltammetry Analysis. RDE voltammetry was used to measure drug-stimulated DA release using a modification of previously published procedures used to measure potassium-stimulated DA release from rat striatal suspensions (Volz et al., 2007) and METH-induced vesicular DA efflux (Volz et al., 2006). Striatal suspensions were placed in the glass chamber at 37°C and a detection current baseline was established as described previously (Volz et al., 2007). The striatal suspensions were then preloaded with 10.2 μ l of 20 μ M DA solution (resulting in a 400 nM [DA] inside the chamber) and, within 3 minutes, the detection current returned to the original baseline. After the DA was preloaded onto the striatal suspensions, a small quantity of assay buffer (in mM: 126 NaCl, 4.8 KCl, 1.3 CaCl₂, 16 sodium phosphate, 1.4 MgSO₄, 11 glucose, pH 7.4) containing 0.25 mM mephedrone, MDMA or METH (resulting in 5 μ M concentrations inside the glass chamber) was added

JPET #184119

to the glass chamber to stimulate DA release. The resulting current outputs caused by DA release were recorded and converted to extravesicular [DA] versus time profiles by calibrating with known [DA] described previously (Volz et al., 2006). The initial velocities of mephedrone-stimulated DA release were calculated from the first 3 s of release and normalized to striatal wet weight as described previously (McElvain and Schenk, 1992; Volz et al., 2007).

Food Training. Rats were restricted to approximately 90% of their free-feeding food quantity and then placed in operant chambers connected to a PC computer running Graphic State software (Coulbourn Instruments, Whitehall, PA). Each chamber was equipped with two retractable levers, one of which was the "active" lever resulting in the delivery of a food pellet, whereas the other lever had no programmed consequences. Training consisted of an overnight 14 h schedule of food reinforcement (45 mg of Rodent Grain food pellets; Bio-Serv Delivering Solutions, Frenchtown, NJ) at FR 1, with only the stimulus-appropriate (drug) lever eliciting the reward

Catheter Implantation. After food training, rats were anesthetized with 90 mg/kg ketamine and 7 mg/kg xylazine (i.p.) and indwelling catheters consisting of a threaded connector, Silastic tubing (10 cm, o.d. 0.51 mm), ProLite polypropylene surgical mesh and dental cement were implanted subcutaneously proximal to the scapula. The distal end of the catheter tubing was inserted into the right jugular vein and was secured to the surrounding tissue with sutures. To maintain catheter patency animals were infused daily with 0.1 ml antibiotic solution containing cefazolin (10.0 mg/ml) dissolved in heparinized saline (70 U/ml; Sigma-Aldrich, St Louis, MO), followed by 0.05 ml infusion of heparin and 0.05 ml of heparinized glycol to lock the catheter.

Self-Administration. After 3 d of recovery, animals were randomly assigned to self-administer either mephedrone (0.24 mg/ 10 μ l infusion), METH (0.24 mg/ 10 μ l infusion) or saline (10 μ l infusion) for 7 or 8 (4 h/d; room temperature 29°C). For each active lever press, an infusion pump (Coulbourn Instruments), connected to a liquid swivel (Coulbourn Instruments) suspended outside the operant

JPET #184119

chamber delivered 10 ul infusion over a 5-s duration through a polyethylene tubing located within a spring leash (Coulbourn Instruments) tethered to the rat. During this period, both levers were retracted. Following the infusion, the levers remained retracted for an additional 20 s. The active lever was counterbalanced within each group. Pressing the inactive lever resulted in no programmed consequences, although it was recorded. Rectal temperatures were measured using a digital thermometer (Physiotemp Instruments, Clifton, NJ) approximately 30 min after the end of each session.

Data Analysis. Statistical analyses between two groups were performed using a two-tailed Student's t-test. Statistical analyses among multi-group data were conducted using one-way ANOVA, followed by a Newman-Keul's post hoc test. Differences among groups were considered significant if the probability of error was less than or equal to 5%. IC_{50} values were determined using a least squares, non-linear regression fit with a minimum of eight data points (determined in triplicate) per curve, and competing drug concentrations ranging from 1 nM to 5 μ M. Lever pressing and mephedrone intake during self-administration was analyzed using a two-way repeated-measures ANOVA with Bonferroni multiple comparisons posthoc analysis. RDE DA release velocities during the first 3 sec were calculated using linear regression. IC_{50} values were determined and all statistical analyses were performed using GraphPad Prism 5 (GraphPad Software, La Jolla, CA).

JPET #184119

Results

Results presented in Fig. 1 reveal that repeated mephedrone injections (4 x 10 or 25 mg/kg/injection, s.c., 2-h intervals, administered in a pattern used frequently in rodent models to mimic psychostimulant “binge” treatment) cause a rapid (within 1 h) decrease in DA and 5HT transporter function, as assessed in striatal and hippocampal synaptosomes, respectively. This decrease was not likely due to residual drug introduced by the original s.c. injections, as other studies have demonstrated that the preparation of synaptosomes “washes” drug from the preparation (Fleckenstein et al., 1997; Kokoshka et al., 1998b). Of note, the IC_{50} value of mephedrone for inhibiting DA uptake was similar to that of METH, while the IC_{50} value for 5HT uptake was similar to that of MDMA (Table 1). Further, mephedrone increased core body temperatures throughout the course of treatment from an average of $37.8 \pm 0.1^* \text{ }^\circ\text{C}$ for saline-treated rats to an average of $39.5 \pm 0.1^*$ and $40.0 \pm 0.1^* \text{ }^\circ\text{C}$ for the rats treated with 10 and 25 mg/kg mephedrone, respectively (*, indicates significant difference from all other groups ($p < 0.05$)). Administration of 4 x 1 mg/kg/injection, or 4 x 3 mg/kg/injection, s.c., 2-h intervals, was without effect on DAT or 5HT transporter function, as assessed 1 h after treatment. Specifically, striatal [^3H]DA uptake levels were 1.7 ± 0.2 , 1.8 ± 0.1 and 1.4 ± 0.1 fmol/ μg protein for saline-, 4 x 1 mg/kg mephedrone-, and 4 x 3 mg/kg mephedrone-treated rats, respectively ($n=7-8$; $p \geq 0.05$). Hippocampal [^3H]5HT uptake levels were 0.8 ± 0.1 , 0.7 ± 0.1 and 0.9 ± 0.1 fmol/ μg protein for saline-, 4 x 1 mg/kg mephedrone-, and 4 x 3 mg/kg mephedrone-treated rats, respectively ($n=7-8$; $p \geq 0.05$). Both doses of mephedrone increased core body temperatures throughout the course of treatment from an average of $37.4 \pm 0.1^* \text{ }^\circ\text{C}$ for saline-treated rats to an average of $38.3 \pm 0.1^*$ and $39.0 \pm 0.1^* \text{ }^\circ\text{C}$ for the rats treated with 4 x 1 and 4 x 3 mg/kg mephedrone, respectively (*, indicates significant difference from all other groups ($p < 0.05$)).

Data presented in Fig. 2 demonstrate that repeated mephedrone administrations (4 x 10 or 25 mg/kg/injection, s.c., 2-h intervals) also caused persistent decreases in hippocampal 5HT transporter function (Fig. 2A) and 5HT (Fig. 2B) levels, as assessed 7 d after treatment. These mephedrone treatments decreased striatal 5HT levels as well (4.0 ± 0.6 , 3.5 ± 0.5 and $2.1 \pm 0.2^* \text{ } \mu\text{g}/\mu\text{g}$ protein for

JPET #184119

saline, 4 x 10 and 4 x 25 mg/kg, respectively (n = 6 – 10); *, indicates significant difference from saline-controls, p < 0.05). In contrast, mephedrone treatment was without effect on striatal DA transporter function (Fig. 2C), DAT immunoreactivity (data not shown), or DA (Fig. 2D) concentrations as assessed 7 d after treatment. Mephedrone increased core body temperatures throughout the course of treatment from an average of $37.7 \pm 0.1^* \text{ }^\circ\text{C}$ for saline-treated rats to an average of $39.2 \pm 0.2^*$ and $39.7 \pm 0.1^* \text{ }^\circ\text{C}$ for the rats treated with 10 and 25 mg/kg mephedrone, respectively (*, indicates significant difference from all other groups (p < 0.05)). Administration of 4 x 1 mg/kg/injection or 4 x 3 mg/kg/injection of mephedrone, s.c., 2-h intervals, did not decrease DA or 5HT levels, as assessed 7 d after treatment. Specifically, striatal DA content was 110.9 ± 6.2 , 119.8 ± 4.5 and $131.3 \pm 7.3 \text{ pg}/\mu\text{g}$ protein, for the saline-, 4 x 1 mg/kg/injection mephedrone-, and 4 x 3 mg/kg/injection mephedrone-treated rats, respectively (n=8; p = 0.08, with DA content being slightly increased after 4 x 3 mg mephedrone/kg/injection). Hippocampal 5HT content was 5.7 ± 0.6 , 6.7 ± 1.5 and $6.6 \pm 0.8 \text{ pg}/\mu\text{g}$ protein, in the saline-, 4 x 1 mg/kg/injection mephedrone-, and 4 x 3 mg/kg/injection mephedrone-treated rats, respectively (n=7-8; p \geq 0.05). Both doses of mephedrone significantly increased core body temperatures throughout the course of treatment from an average of $37.4 \pm 0.1^* \text{ }^\circ\text{C}$ for saline-treated rats to an average of $38.8 \pm 0.2^*$ and $39.0 \pm 0.1^* \text{ }^\circ\text{C}$ for the rats treated with 1 and 3 mg/kg mephedrone, respectively (*, indicates significant difference from the saline-treated rats (p \leq 0.05)).

In order to determine brain and plasma mephedrone levels, a method was developed using liquid chromatography-mass spectrometry. Using this assay, results revealed plasma levels of 384.2 ± 62.2 , and $1294.3 \pm 145.5 \text{ ng}$ mephedrone/ml plasma as assessed 1 h after 4 x 10 or 25 mg/kg/injection (s.c., 2-h intervals), respectively. Whole brain levels of 2.1 ± 0.2 and $7.8 \pm 0.9 \text{ ng}$ mephedrone/mg tissue were found 1 h after 4 x 10, 25 mg/kg/injection (s.c., 2-h intervals), respectively.

JPET #184119

DA release was assessed after application of 5.0 μ M of METH, mephedrone, or MDMA onto striatal suspensions that were preloaded with DA. Results revealed that the initial velocities (determined over the first 3 s) were $0.29^* \pm 0.01$, $0.25 \pm 0.01^*$ and $0.16 \pm 0.01^*$ nmol DA/(s*g wet weight tissue) for METH, mephedrone and MDMA, respectively ($F(2, 4071) = 85.2509$, *, indicates significant difference from all other groups, $p \leq 0.05$). The maximal values for DA release for METH, mephedrone and MDMA were $3.8 \pm 0.6^*$, $2.7 \pm 0.2^*$ and $1.7 \pm 0.2^*$ nmol DA/g weight tissue, respectively (*, indicates significant difference from all other groups ($p \leq 0.05$)).

Fig. 4A demonstrates that rodents self-administer mephedrone. Whereas saline self-administering animals ($n=10$) decreased pressing from day 1 of self-administration to day 8, mephedrone self-administering rats ($n=13$) increased pressing (drug x day interaction: $F(7, 147)=24.88$, $p<0.05$; Figure 4A). Mephedrone self-administering animals increased daily drug intake from 1.77 ± 0.15 mg on day 1 to 6.78 ± 1.00 mg on day 8 ($F(7, 84)=17.59$, $p<0.05$). Discrimination of the reinforced lever from the inactive lever increased from a ratio of 2.65: 1 reinforced presses per inactive press on day 1 to 10.71: 1 reinforced presses per inactive press on day 8 in mephedrone self-administering rats. Approximately 85% of mephedrone self-administering rats increased drug intake on 3 or more consecutive days. Mephedrone self-administration also increased core body temperature (assessed 30 min after the end of each daily session) from an average of 37.3 ± 0.1 °C for saline-controls to an average of $38.0 \pm 0.1^*$ °C for mephedrone self-administering rats (*, indicates significant difference from saline-controls ($p < 0.05$)).

For comparison with data presented in Fig. 4A, animals were allowed to self-administer METH under identical conditions (e.g., same dosing, duration of sessions, etc.) as were utilized to study mephedrone self-administration (Fig. 4B). Again saline self-administering animals ($n=8$) decreased pressing from day 1 of self-administration to day 7 while METH self-administering rats ($n=8$) rapidly acquired stable lever-pressing behavior ($F(6,84)=23.63$, $p<0.05$). Daily drug intake averaged 2.55 ± 0.06 mg METH/session across the 7 d of treatment). Discrimination of the reinforced lever from the

JPET #184119

inactive lever averaged a ratio of 10.1:1 reinforced presses per inactive press in the METH self-administering animals. METH self-administration also increased core body temperature (assessed 30 min after the end of each daily session) from an average of 37.6 ± 0.1 °C for saline-controls to an average of $38.2 \pm 0.2^*$ °C for METH self-administering rats (*, indicates significant difference from saline-controls ($p < 0.05$)).

JPET #184119

Discussion

The stimulant/hallucinogen, mephedrone, has received recent international attention. Most abusers report that in terms of its subjective effects, the agent most resembles MDMA (Carhart-Harris et al., 2011). However, some abusers also liken its subjective effects to those of cocaine (Carhart-Harris et al., 2011). Of further interest are reports that, unlike MDMA (First and Tasman, 2010), some mephedrone abusers tend to binge on mephedrone (Schifano et al., 2010; but see also, Carhart-Harris et al., 2011).

The present study demonstrates that mephedrone has several pharmacological characteristics in common with other well-characterized psychostimulants such as MDMA and METH. First, the IC_{50} value for inhibition of striatal synaptosomal DA uptake resembles that of METH, while the IC_{50} values for inhibition of hippocampal synaptosomal 5HT uptake resembles that of MDMA. Second, and like METH and MDMA (Fleckenstein et al., 1999; Metzger et al., 2000; Haughey et al., 2000; Hansen et al., 2002), repeated high-dose injections of mephedrone, administered in a regimen designed to mimic "binge" use in humans, causes rapid decreases in DA and 5HT transporter function. Third, each of these agents promotes stimulant-induced hyperthermia.

Although METH and MDMA share many characteristics, one important factor that distinguishes METH and MDMA is that the latter causes persistent serotonergic deficits in rat and human models, while largely sparing dopaminergic neurons (Stone et al., 1986; Schmidt and Kehne, 1990; McCann et al., 1994; Reneman et al., 2001). In this respect, mephedrone more closely resembles MDMA. This is of interest, as most individuals who abuse mephedrone report subjective effects reminiscent of MDMA (Schifano et al., 2010; Carhart-Harris et al., 2011), suggesting similarities in the underlying mechanisms of action of these agents.

Despite the similarities noted above with the effects of MDMA, mephedrone causes greater DA release as assessed in a striatal suspension preloaded with equimolar concentrations of DA. In fact,

JPET #184119

in response to application of 5 μ M drug (a concentration selected based, in part, upon studies by Clausning et al. (1995) wherein extracellular brain levels in the μ M range were demonstrated after amphetamine administration) the *in vitro* DA-release capacity of mephedrone approaches that of METH. Although this study is limited in that only a single drug concentration was employed, its results are consistent with recent microdialysis findings by Kehr et al. (in press) that mephedrone caused DA release (albeit the present study examined DA release from a striatal suspension) and mephedrone caused greater DA release than MDMA. These data are also consistent with reports by some users that the subjective effects of mephedrone resemble METH, or like a combination of MDMA and cocaine (Carhart-Harris et al., 2011). Finally, these data are consistent with our finding that mephedrone is readily self-administered by rats (Fig. 4). Of note, METH is a potent DA-releasing agent (Bowyer et al., 1993; Kuczenski et al., 1995; Tata and Yamamoto, 2007) and its high-dose administration causes persistent dopaminergic deficits (for review, see Hanson et al., 2004; Yamamoto and Bankston, 2005; Tata and Yamamoto, 2007, and references therein). Since mephedrone has DA-releasing capability resembling METH and yet does not cause dopaminergic deficits, it is of significant interest in terms of studying the differential mechanisms understanding the long-term damage caused by these stimulants.

Of note, mephedrone concentrations were evaluated and detected in both rat plasma and brain samples following the controlled administration of mephedrone. Mean whole brain levels of 2.1 ± 0.2 ng mephedrone/mg tissue were found 1 h after 4 x 10 mg/kg/injection (s.c., 2-h intervals). This value compares with mean brain levels of 4.3 ± 0.5 ng/mg tissue as reported 1 h after 4 x 5 mg/kg/injection of METH (s.c., 2-h intervals; Truong et al., 2005). However, any comparison between these METH and mephedrone data must be made very cautiously as studies designed specifically to compare pharmacokinetics are necessary to address differences and similarities between the drugs.

Given the DA-releasing capacity of mephedrone, the finding that mephedrone readily penetrates the blood-brain barrier, mephedrone is readily self-administered by rats, and that the reinforcing effects of

JPET #184119

psychostimulants are associated with increases in brain DA levels (Volkow et al., 1999), it is reasonable to speculate that mephedrone may have significant abuse liability. Indeed, results presented in Fig. 4A demonstrate that mephedrone is readily self-administered, as assessed over 8 d of exposure to 4-h sessions (0.24 mg/kg/infusion). For comparison, the ability of METH to elicit self-administration under identical experimental conditions was assessed. Results confirmed numerous reports that, like mephedrone, METH is readily self-administered. However, and in contrast to effects of mephedrone, lever-pressing behavior did not increase over the 8-d duration of the experiment, possibly due to the increased stereotypy associated with this high infusion dose. Several factors likely account for this differential response including differences in pharmacokinetics, DA-releasing capabilities, and potential long-term consequence of repeated exposures (e.g., repeated high-dose METH administrations cause persistent dopaminergic damage, whereas data presented in Figs. 2C and 2D reveal that repeated high-dose mephedrone administrations do not cause such deficits).

In summary, mephedrone is a unique psychostimulant of abuse that shares pharmacological properties similar to, and yet distinct from, both METH and MDMA. Its ability to cause subjective effects resembling MDMA reportedly likely contributes to its abuse. However, its ability to cause DA release greater than MDMA may be particularly problematic in that, in comparison to MDMA, this drug may have enhanced abuse liability more resembling that of DA-releasing agents such as METH. Prior to this report, clinical and anecdotal reports have been the primary source of information concerning the stimulant. As noted above, this lack of reliable information is particularly problematic for public health policy makers and law enforcement organizations as they attempt to develop and implement appropriate strategies for dealing with the escalating recreational use of this substance and products that contain mephedrone and related drugs. In fact, the US Drug Enforcement Administration recently appealed for information concerning mephedrone and its analogs. Thus, additional studies are needed both to further investigate the impact of mephedrone, but also the various synthetic analogs that are an important public health concern.

JPET #184119

Authorship Contributions

Participated in research design: Hadlock, Webb, Chu, McFadden, Gibb, Hanson, and Fleckenstein.

Conducted experiments: Hadlock, Webb, Chu, McFadden, Ellis, Allen, Andrenyak, Veira-Brock, German, Conrad, and Hoonakker.

Contributed new reagents or analytical tools: Andrenyak and Wilkins.

Performed data analysis: Hadlock, Webb, Chu, McFadden, Andrenyak, Veira-Brock, German, Wilkins, and Fleckenstein.

Wrote or contributed to the writing of the manuscript: Hadlock, Webb, Gibb, Hanson, and Fleckenstein.

JPET #184119

References

Advisory Council on the Misuse of Drugs/ACMD (2010) Advisory Council on the Misuse of Drugs on Consideration of the Cathinones. <http://www.homeoffice.gov.uk/publications/drugs/acmd1/acmd-cathinodes-report-2010>, accessed 18 August 2010.

Bowyer JF, Gough B, Slikker W Jr, Lipe GW, Newport GD, Holson RR (1993). Effects of a cold environment or age on methamphetamine-induced dopamine release in the caudate putamen of female rats. *Pharmacol Biochem Behav* 44: 87-98.

Carhart-Harris RL, King LA, Nutt D (2011) A web-based survey on mephedrone. *Drug Alcohol Depend.* doi: 10.1016/j.drugalcdep.2011.02.011.

Clausing P, Gough B, Holson RR, Slikker W Jr, Bowyer JF. (1995) Amphetamine levels in brain microdialysate, caudate/putamen, substantia nigra and plasma after dosage that produces either behavioral or neurotoxic effects. *J Pharmacol Exp Ther* 274: 614-621.

Cressey D (2010) Mephedrone on borrowed time. *Nature* doi:10.1038/news.2010.159.

First MB and Tasman A (2010) *Clinical Guide to the Diagnosis and Treatment of Mental Disorders*. Wiley and Sons, West Sussex.

Fleckenstein AE, Haughey HM, Metzger RM, Kokoshka JM, Riddle EL, Hanson JE, Gibb JW, Hanson GR (1999) Differential effects of psychostimulants and related agents on dopaminergic and serotonergic transporter function. *Eur J Pharmacol* 382: 45-49.

Fleckenstein AE, Metzger RR, Wilkins DG, Gibb JW, Hanson GR (1997) Rapid and reversible effects of methamphetamine on dopamine transporters. *J Pharmacol Exp Ther* 282: 834-838.

JPET #184119

Fleckenstein AE, Haughey HM, Metzger RR, Kokoshka JM, Riddle EL, Hanson JE, Hanson GR, (1999) Differential effects of psychostimulants and related agents on dopaminergic and serotonergic transporter function. *Eur J Pharmacol* 382: 45-49.

Guilarte TR, Nihei MK, McGlothan JL, Howard AS (2003). Methamphetamine-induced deficits of brain monoaminergic neuronal markers: distal axotomy or neuronal plasticity. *Neuroscience* 122: 499-513.

Gygi MP, Fleckenstein AE, Gibb JW, Hanson GR (1997) Role of endogenous dopamine in the neurochemical deficits induced by methcathinone. *J Pharmacol Exp Ther* 283: 1350-1355.

Hansen JP, Riddle EL, Sandoval V, Brown JM, Gibb JW, Hanson GR, Fleckenstein AE (2002) Methylenedioxymethamphetamine decreases plasmalemmal and vesicular dopamine transport: Mechanisms and implications for neurotoxicity. *J Pharmacol Exp Ther* 300: 1093-1100.

Hanson GR, Rau KR, Fleckenstein AE (2004) The methamphetamine experience: A NIDA partnership (2004) *Neuropharmacol* 47: 92-100.

Haughey HM, Fleckenstein AE, Metzger RM, Hanson GR (2000). The effects of methamphetamine on serotonin transporter activity: Role of dopamine and hyperthermia. *J Neurochem* 75: 1608-1617.

Hotchkiss AJ, Morgan ME, Gibb JW (1979) The long-term effects of multiple doses of methamphetamine on neostriatal tryptophan hydroxylase, tyrosine hydroxylase, choline acetyltransferase and glutamate decarboxylase activities. *Life Sci* 25: 1373-1378.

Kehr J, Ichinose F, Yoshitake S, Goiny M, Sievertsson T, Nyberg F, Yoshitake T. Mephedrone, compared to MDMA (ecstasy) and amphetamine, rapidly increases both dopamine and serotonin levels in nucleus accumbens of awake rats. *Br J Pharmacol*. 2011 May 26. doi: 10.1111/j.1476-5381.2011.01499.x. [Epub ahead of print]

JPET #184119

Kokoshka JM, Metzger RR, Wilkins DG, Gibb JW, Hanson GR, Fleckenstein AE (1998a) Methamphetamine treatment rapidly inhibits serotonin, but not glutamate, transporters in rat brain. *Brain Res* 799: 78-83.

Kokoshka JM, Vaughan RA, Hanson GR, Fleckenstein AE (1998b) Nature of methamphetamine-induced rapid and reversible changes in dopamine transporters. *Eur J Pharmacol* 361: 269-275.

Krasnova IN, Cadet JL (2009) Methamphetamine toxicity and messengers of death. *Brain Res Rev* 60: 379-407.

Kuczenski R, Segal DS, Cho AK, Melega W (1995) Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. *J Neurosci* 15: 1308-1317.

McCann UD, Ridenour A, Shaham Y, Ricaurte GA (1994) Serotonin neurotoxicity after (+/-)3,4-methylenedioxyamphetamine (MDMA; 'Ecstasy'): a controlled study in humans. *Neuropsychopharmacol* 10: 129-138.

McCann UD, Wong DF, Yokoi F, Villemagne V, Dannals RF, Ricaurte GA (1998) Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: Evidence from positron emission tomography studies with [¹¹C]WIN-35,428. *J Neurosci* 18: 8417-8422.

McElvain JS, Schenk JO (1992) Blockade of dopamine autoreceptors by haloperidol and the apparent dynamics of potassium-stimulated endogenous release of dopamine from and reuptake into striatal suspensions in the rat. *Neuropharmacol* 31: 649-659.

Mereu GP, Pacitti C, Argiolas A (1983) Effect of (-)-cathinone, a khat leaf constituent, on dopaminergic firing and dopamine metabolism in the rat brain. *Life Sci* 32:1383-1389.

JPET #184119

Metzger RR, Haughey HM, Wilkins DG, Gibb JW, Hanson GR, Fleckenstein AE (2000) Methamphetamine-induced rapid and reversible decrease in dopamine transporter function: Role of dopamine and hyperthermia. *J Pharmacol Exp Ther* 295: 1077-1085.

Morris K (2010) UK places generic ban on mephedrone drug family. *Lancet* 375: 1333-1334.

Nash JF, Yamamoto BK. (1992) Methamphetamine neurotoxicity and striatal glutamate release: comparison to 3,4-methylenedioxymethamphetamine. *Brain Res* 581:237-43.

Reneman L, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeten GJ, Booij J (2001) Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. *Arch Gen Psychiatry*. 58: 901-906.

Ricaurte GA, Schuster CR, Seiden LS (1980) Long-term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in the rat brain: a regional study. *Brain Res* 193: 153-163.

Schifano F, Albanese A, Fergus S, Stair JL, Deluca P, Corazza O, Davey Z, Corkery J, Siemann H, Scherbaum N, Farre M, Torrens M, Demetrovics Z, Ghodse AH (2010) Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. *Psychopharmacol* 214: 593-602.

Schmidt CJ, Kehne JH (1990) Neurotoxicity of MDMA: neurochemical effects. *Ann N Y Acad Sci* 600: 665-681.

Scott JC, Woods SP, Matt GE, Meyer RA, Heaton RK, Atkinson JH, Grant I (2007) Neurocognitive effects of methamphetamine: a critical review and meta-analysis. *Neuropsychol Rev* 17: 275-97.

JPET #184119

Sekine Y, Iyo Y, Matsunaga T, Tsukada H, Okada H, Yoshikawa E, Futatsubashi M, Takei N, Mori N (2001) Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. *Am J Psychiatry* 158: 1206-1214.

Sparago M, Wlos J, Yuan J, Hatzidimitriou G, Tolliver J, Dal Cason TA, Katz J, Ricaurte G. (1996) Neurotoxic and pharmacologic studies on enantiomers of the N-methylated analog of cathinone (methcathinone): a new drug of abuse. *J Pharmacol Exp Ther* 279: 1043-1052.

Stone DM, Stahl DC, Hanson GR, Gibb JW (1986) The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) on monoaminergic systems in the rat brain. *Eur J Pharmacol* 128: 41-48.

Tata DA, Yamamoto BK (2007) Interactions between methamphetamine and environmental stress: role of oxidative stress, glutamate and mitochondrial dysfunction. *Addiction* 102 Suppl 1:49-60.

Truong JG, Wilkins DG, Baudys J, Crouch DJ, Johnson-Davis KL, Gibb JW, Hanson GR, Fleckenstein AE (2005) Age-dependent methamphetamine-induced alterations in vesicular monoamine transporter-2 function: implications for neurotoxicity. *J Pharmacol Exp Ther* 314: 1087-1092.

Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Wong C, Hitzemann R, Pappas NR (1999) Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D2 receptors. *J Pharmacol Exp Ther* 291: 409-415.

Volkow ND, Chang L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi, D, Sedler MJ, Gatley, SJ, Hitzemann R, Ding YS, Logan J, Wong C, Miller EN (2001) Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry* 158: 377-382.

JPET #184119

Volz TJ, Farnsworth SJ, King JL, Riddle EL, Hanson GR, Fleckenstein AE (2007) Methylphenidate administration alters vesicular monoamine transporter-2 function in cytoplasmic and membrane-associated vesicles. *J Pharmacol Exp Ther* 323: 738-745.

Volz TJ, Hanson GR, Fleckenstein AE (2006) Measurement of kinetically resolved vesicular dopamine uptake and efflux using rotating disk electrode voltammetry. *J Neurosci Methods* 155: 109-115.

Wagner GC, Ricaurte GA, Seiden LS, Schuster CR, Miller RJ, Westley J (1980) Long-lasting depletions of striatal dopamine and loss of dopamine uptake sites following repeated administration of methamphetamine. *Brain Res* 181:151-160.

Yamamoto BK, Bankson MG (2005) Amphetamine neurotoxicity: cause and consequence of oxidative stress. *Crit Rev Neurobiol.* 17: 87-117.

JPET #184119

FOOTNOTES

This work was supported by grants from the National Institute on Drug Abuse [DA00869, DA04222, DA13367, DA11389, DA019447, and DA00378].

JPET #184119

Figure Legends

Fig. 1. Repeated mephedrone injections rapidly (within 1 h) decrease hippocampal synaptosomal (A) 5HT uptake and striatal synaptosomal (B) DA uptake. Rats received mephedrone (4 x 10 or 25 mg/kg/injection; s.c.; 2-h intervals) or saline (1 ml/kg/injection; s.c.; 2-h intervals) and were sacrificed 1 h after the final injection. Columns represent means and vertical lines 1 SEM determinations in 6-10 rats. *, indicates significant difference from saline controls ($p < 0.05$).

Fig. 2 Repeated mephedrone injections cause persistent decreases in (A) hippocampal synaptosomal 5HT uptake and (B) hippocampal 5HT content, but not in (C) striatal synaptosomal DA uptake or (D) striatal DA content as assessed 7 d after treatment. Rats received mephedrone (4 x 10 or 25 mg/kg/injection; s.c.; 2-h intervals) or saline vehicle (1 ml/kg/injection; s.c.; 2-h intervals) and were sacrificed 7 d later. Tissues were assayed as described in "DA and 5HT concentrations," and "Synaptosomal [3 H]DA and [3 H]5HT uptake" (see **Methods** above). Columns represent the means and vertical lines 1 SEM determinations in 6-10 rats. *, indicates significant difference from all other groups ($p < 0.05$).

Fig. 3. Mephedrone causes DA release from a striatal suspension. 5.0 μ M of METH, mephedrone, or MDMA were applied to a striatal suspension that was preloaded with DA (see Methods, $n = 7-11$). The initial velocity of DA release (determined over the first 3 s) for METH, mephedrone and MDMA were $0.29 \pm 0.01^*$, $0.25 \pm 0.01^*$ and $0.16 \pm 0.01^*$ nmol/(s*g wet weight tissue), respectively (*, indicates significant difference from all other groups, $p < 0.05$, $f(2, 4071)=85.2509$). The maximal DA release for METH, mephedrone and MDMA were $3.8 \pm 0.6^*$, $2.7 \pm 0.2^*$ and $1.7 \pm 0.2^*$ nmol/g weight weight tissue, respectively. *, indicates significant difference from all other groups ($p < 0.05$).

Fig. 4. (A) Mephedrone and (B) METH are self-administered by rats. Rats were food-trained as described in Methods. After catheter implantation, rats were given access (4-h sessions; 7-8 days) to saline (10 μ l/infusion), mephedrone (0.24 mg/ 10 μ l infusion), or METH (0.24 mg/ 10 μ l infusion)

JPET #184119

according to an FR1 schedule of reinforcement as described in Methods. * indicates significant difference from saline controls ($p < 0.05$).

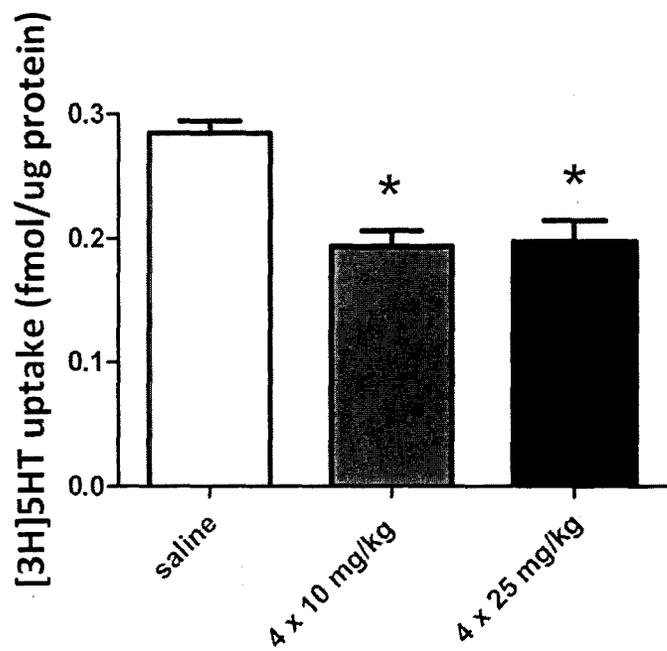
JPET #184119

TABLE LEGEND

Table 1. IC₅₀ values for striatal DA uptake and hippocampal 5HT uptake in synaptomes. IC₅₀ values represent the means of at least three independent experiments, and were obtained as described in Methods. N/A – not assessed. ^a, values reported previously (Fleckenstein et al., 1997).

Drug	DA uptake IC ₅₀ (nM)	5HT uptake IC ₅₀ (nM)
Mephedrone	467 ± 17	558 ± 48
MDMA	1216 ± 263	291 ± 36
Cocaine	1032 ± 96	1036 ± 137
METH	291 ± 4 ^a	N/A

A



B

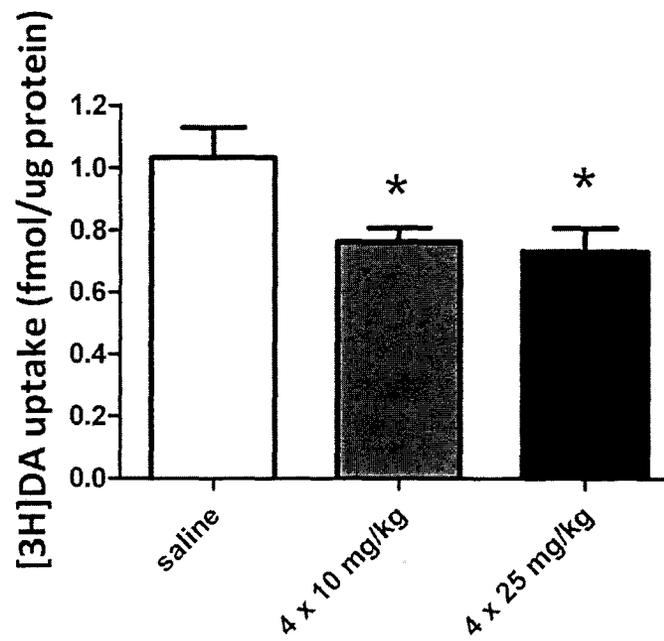


Figure 1

000543

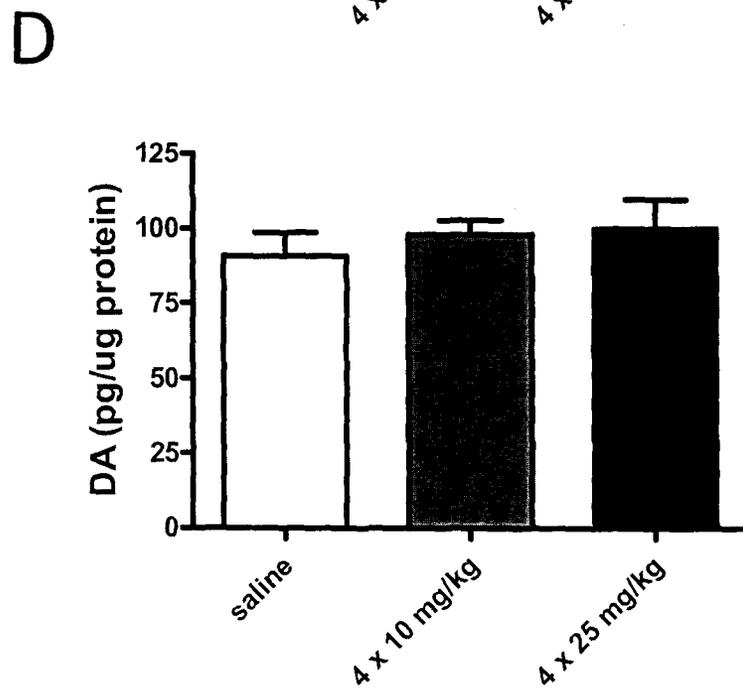
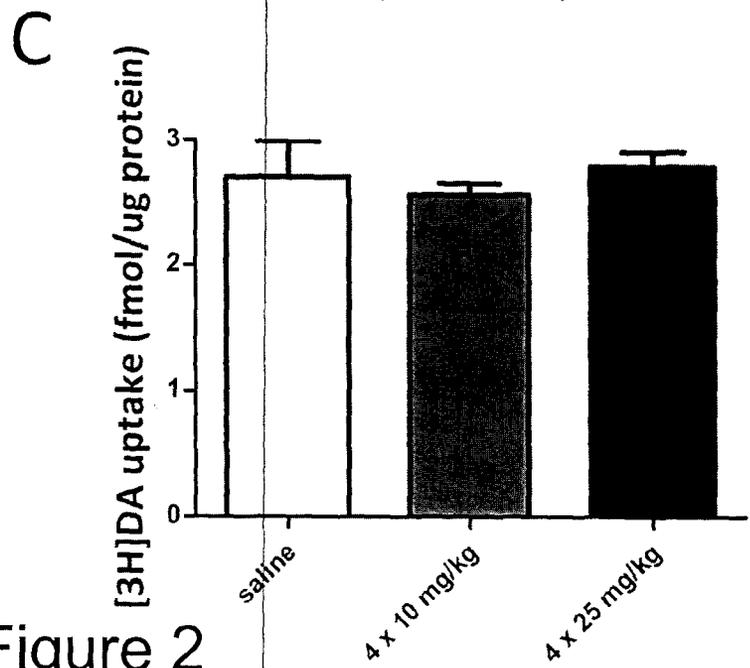
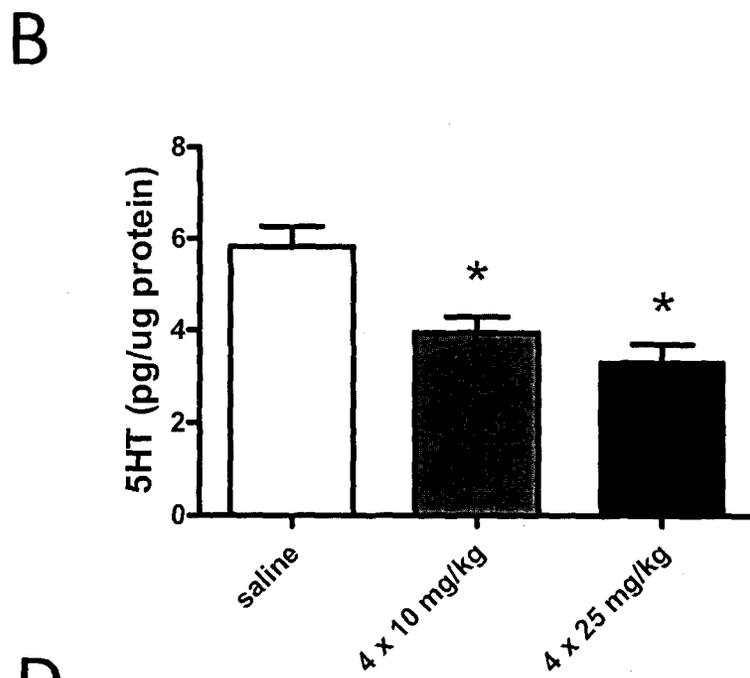
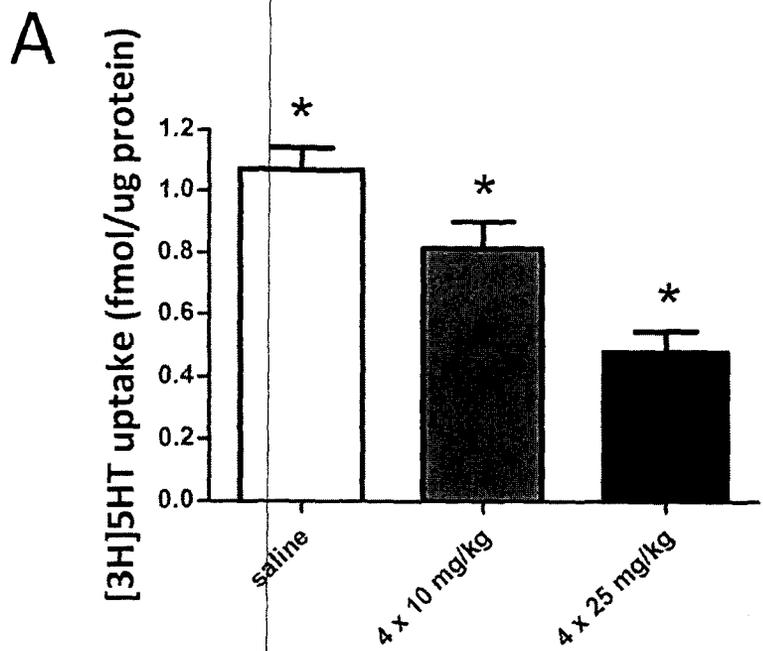


Figure 2

000544

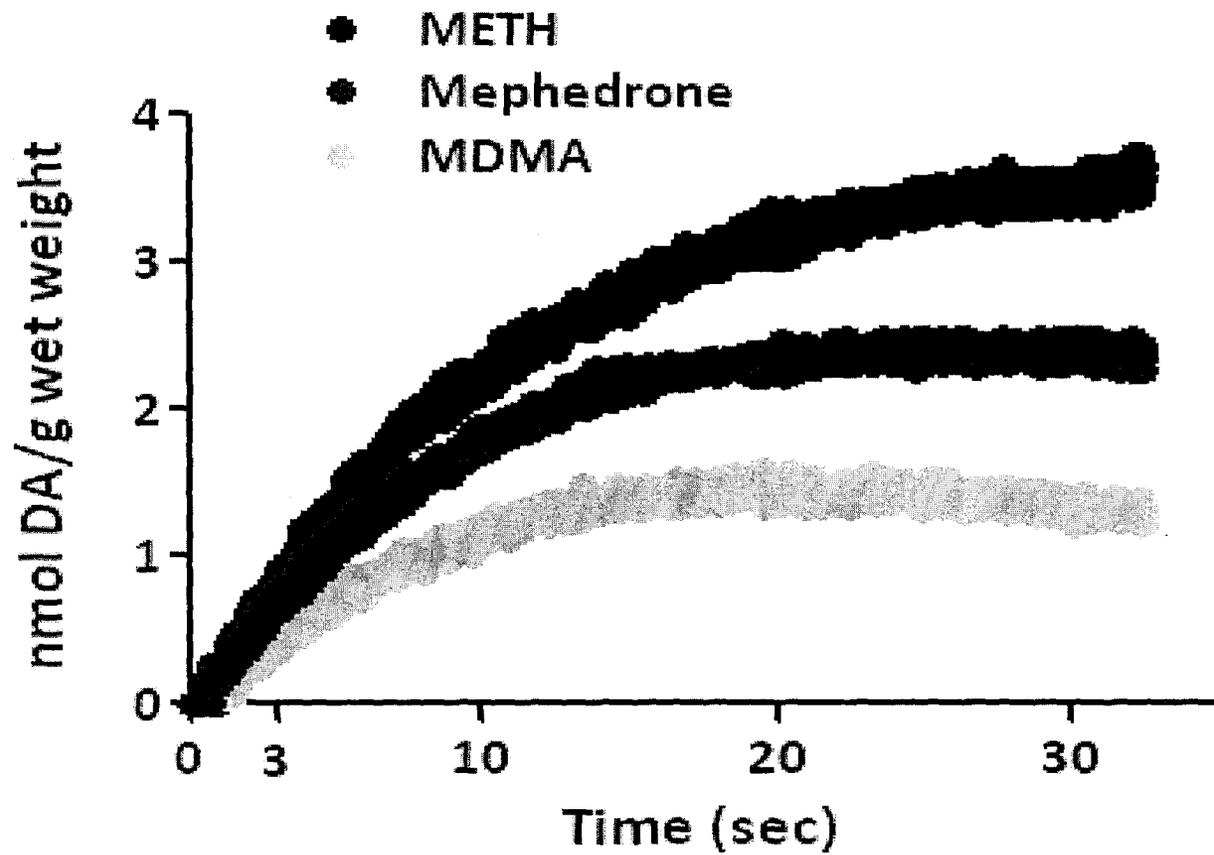
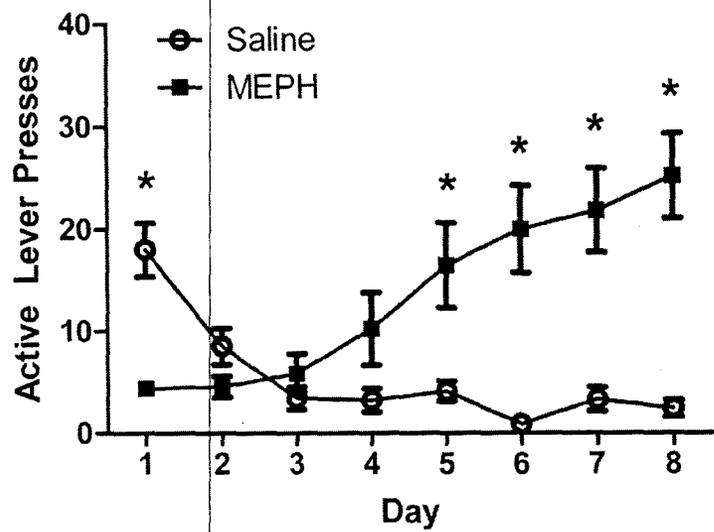


Figure 3

A



B

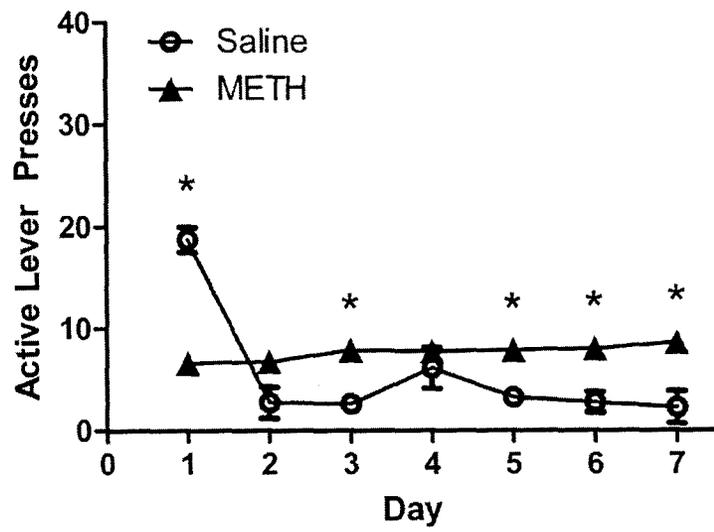


Figure 4

74



For action: Revisions to MDPV Triage Statement
Tara Phillips to: Nathan Isotalo

2012-04-17 10:51 AM

History: This message has been replied to.

Hi Nathan,

I have reviewed the draft MDPV Triage Statement and request changes according to the attached documents. Sorry for the separate files per page; I had problems with the document feeder.

As discussed yesterday, please revise at your earliest convenience. In addition, please draft the *Notice to interested parties*.

Prior to submitting the revised Triage Statement and the Notice to me, please review and edit the documents for quality per the checklist that we had discussed previously and that I will forward you in a few minutes.

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-04-17 10:45 AM -----



Page 1.pdf



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95



Treasury Board of Canada Secretariat

Secrétariat du Conseil du Trésor du Canada

s.21(1)(a)
s.21(1)(b)

Triage Statement Form

Section I: Overview

Security classification
Protected B

Date received by RAS: May 2012

Title of the Regulatory Proposal: **Regulation of MDPV**

Sponsoring Regulatory Organization: Health Canada

Statutory Authority: *Controlled Drugs and Substances Act*

Approximate date of submission of regulatory proposal to PCO-OIC:

Use title similar to current title of reg. proposal for tapentadol

Issue

Over the past couple of years, in North America, abuse of a new designer drug "bath salts" has steadily been increasing. These synthetic products are abused for their stimulant like effects.

Substance abuse and police/border seizures of Internet marketed products known as "bath salts" have risen sharply in the United States the past few years and is slowly on the rise in Canada

however, does not yet point to widespread use of "bath salt" products in the general population.

These synthetic "bath salts"

Canadian Service Border Agency (CBSA) Laboratory has seen an increase in the amount of samples MDPV being samples for analysis. Between January 2010 and April 2011 about 16 samples had tested positive for (MPDV) while between April 2011 and March 2012, 24 samples had tested positive. Two of these samples were taken from two seizures of 10 barrels each of 185 kg pure MDPV.

These synthetic "bath salts" are not traditional epsom salt (hydrated magnesium sulphate) consumer products used for bathing relaxation which fall under the definition of consumer product of the Canada Consumer Product Safety Act (CCPSA) but are new designer drug products that be similar in physical appearance.

products may contain either mephedrone, methylone and/or 3,4-methylenedioxypyrovalerone (MDPV) and may be sold over the Internet and in drug paraphernalia head shops in small package sizes and labelled as "bath salts" or "plant food", and "not for human consumption" in order for them to appear legal. There currently exist no legitimate therapeutic, scientific, industrial or commercial uses for these synthetic "bath salt" products or MDPV in Canada.

In Canada, both mephedrone and methylone are considered controlled substances under the *Controlled Drugs and Substances Act (CDSA)* as they are synthetic analogs of the naturally occurring β -ketone amphetamine analogue of the *Catha edulis* plant, cathinone, which is a Schedule III listed controlled substance.

footnote following "methylone" in what is now the first paragraph.

Handwritten notes and annotations: "Para #1", "Run on sentence", "move sentence to international para at end of issue section", "law enforcement reports of", "typically referred to as", "found to contain", "insert footnote with description of epsom salts, both therapeutic and other uses", "although they 'Bath salts' have been", "Note that it is Canada Consumer Product Safety Act (CCPSA)", "are available on alternative lifestyle stores", "are no known", "use CDSA spelling", "Item 19, pls double check this ref", "approximately", "with references to applicable legislation"

if MDMA is an amphetamine, is this separate reference required?

has some sp.

MDPV belongs to a group of substances called phenylethylamines which are ~~β-ketone~~ analogs of amphetamines and 3,4-methylenedioxymethamphetamine (MDMA). Despite MDPV's chemical similarities to the amphetamine cathinone and other controlled substances such as phenmetrazine and pyrovalerone, ~~Currently, MDPV is not considered to be scheduled under the CDSA.~~ ^{a controlled substance}

Synthetic "bath salts"

^{these} These products may be abused by ingestion, snorting, injection or rectal administration. Reported adverse effects of ~~abused bath salt~~ ^{MDPV} products may include: hypertension, paranoia, delusions, hallucinations, tachycardia, serotonin syndrome, insomnia, psychosis, suicidal thoughts, and self-harmful tendencies such as self-mutilation and ~~in some cases~~ ^{has been} death. It is often reported that when abuse is stopped that drug users experience intense cravings, a result of their physical dependence on the drug and during use tolerance thresholds are often exceeded so that more drug is needed to create the stimulant "high". ^{as}

please rework for clarity

^{of} ^{Part I} ^{on Health} As there exist significant risks to both personal and public safety and security from the ~~serious~~ ^{availability} of abuse, addiction liability and adverse effects associated with MDPV, a ~~Notice to Interested Parties on the regulatory proposal~~ ^{Part I seeking stakeholder input to indicate Health} will be published in *Canada Gazette*. ~~Canada's intent to add 3,4-methylenedioxypyrovalerone (MDPV) its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and ~~insert paragraph~~ to the Schedule to Part J of the Food and Drug Regulations (FDR) under the Food and Drugs Act (FDA).~~ ^{of}

~~Insert paragraph~~ ^{of} on international context. Objectives

To add 3,4-methylenedioxypyrovalerone (MDPV) its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and as item 1(19) to the Schedule to Part J to the FDR. ^{Scheduling MDPV under CDSA} ~~(Such action would prohibit all activities, e.g., possession, importation, and exportation, involving MDPV, its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues or any related products unless authorized under the NCR or a Ministerial exemption as per section 56 of the CDSA.)~~ ^{Insert}

What did you mean by reference to NCR and section 56? I don't see the relationship to this proposal.

Description

Health Canada ^{es to add} ~~is~~ proposing to add 3,4-methylenedioxypyrovalerone (MDPV), its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues ^{added} to Schedule IV to the CDSA and as item 1(19) to the Schedule to Part J to the FDR. ^{of}

This sentence doesn't need to be here. You already have it in the description. This section is meant to be ~~added~~ ^{higher-level}.

The CDSA sets out penalties for illegal activities involving substances listed in its Schedules and the Regulations under the CDSA establish tight controls on the movement of regulated substances with a view to reducing abuse and diversion to the illicit market. As such, scheduling will enable law enforcement to respond to illegal activities. The ultimate goal of this regulatory proposal is to reduce the risks to health and safety of Canada. 000549 ^{ince} availability

Canada

Page(s) 000550 to\à 000556

**Is(Are) exempted pursuant to section(s)
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**

96



Fw: re methylone
Nathan Isotalo to: Tara Phillips

2012-04-17 01:40 PM

Hi Tara,
fyi- mephedrone was also considered item 1 of Sch. III to the CDSA also.

Nathan.

----- Forwarded by Nathan Isotalo/HC-SC/GC/CA on 2012-04-17 01:39 PM -----

From: Nathan Isotalo/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-04-17 01:30 PM
Subject: Fw: re methylone

Good afternoon, Tara;

fyi- Methylone is item 1 of Sch III to CDSA. Nathan.

----- Forwarded by Nathan Isotalo/HC-SC/GC/CA on 2012-04-17 01:25 PM -----

From: Evelyn Soo/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Cc: Status/HC-SC/GC/CA@HWC
Date: 2012-03-09 11:56 AM
Subject: Re: re methylone

Hi Nathan

Yes, status is CONTROLLED under item 1 of Schedule III to the CDSA.

Evelyn

Evelyn C Soo, PhD
A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
environnementale et de la sécurité des consommateurs (DGSESC)
Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
evelyn.soo@hc-sc.gc.ca
Telephone | Téléphone 613-954-1758
Government of Canada | Gouvernement du Canada

Nathan Isotalo Good morning, Evelyn do you have a status dec... 2012-03-09 11:22:02 AM

From: Nathan Isotalo/HC-SC/GC/CA
To: Evelyn Soo/HC-SC/GC/CA@HWC
Date: 2012-03-09 11:22 AM
Subject: re methylone

Good morning, Evelyn

do you have a status decision on "methylone"? I suspect that it would be an Sch. III analogue of
cathinone. Chem name: 3,4-methylenedioxy-N-methylcathinone.

thank you. Nathan.

97



Re: Checklist
Nathan Isotalo to: Tara Phillips

2012-04-17 03:35 PM

Good afternoon, Tara;

I have gone over your comments. As I was asked for a quick turn -around time, the triage was a quick and dirty, I regret there were some typos.

I will make a future effort to further "polish" my work by giving it a final unhurried read through before sending.

For your information, I have addressed a few of your raised points below.

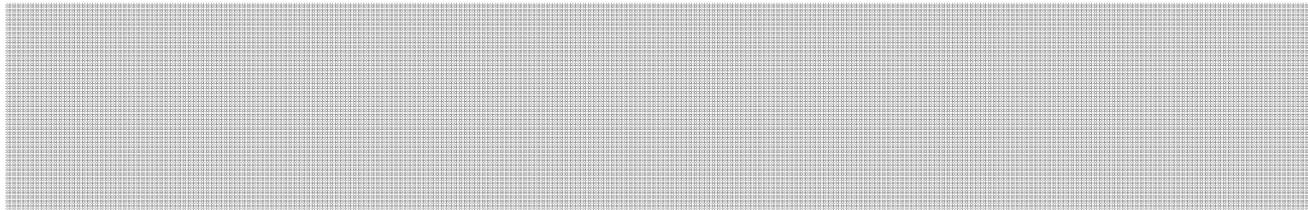
As for the acronyms, I have seen CBSA referred to as both Canada Service Border Agency and Canada Border Service Agency in documentation. I usually refer to it as the latter as per CSTD intranet website. I have changed the order. As for the recent Product Safety Act, most refer to it in passing as the Consumer Product Safety Act (shorter). I have added the Canada for consistency with the name upon Royal Assent.

As for your requested confirmation, I sent you earlier status decisions for methylone and mephedrone; both fall under item I of Sch III to CDSA not item 19.

Your identified "run on" phrase is compound or complex. Compound/complex sentences can serve a purpose and I was o.k. with it as written but since, you would like to have it split up, I have shortened to separate the ideas.

I noticed that for the impact on society and culture, item number 3 of triage, the triage template mentions that special consideration should be given to vulnerable social and economic groups such as Aboriginal peoples, official-language minorities, lower income Canadians, recent immigrants, and groups affected on the basis of age, gender, race or culture. I only attempted to capture this requirement for consideration of vulnerable groups by writing that these (vulnerable) groups may become attracted to the drugs as their availability and popularity increase which is a likely impact so what I wrote is not necessarily out of scope. I remember seeing a reference to aboriginals somewhere, so I will check to see if there is any more specific data that we might consider.

s.21(1)(a)
s.21(1)(b)



Nathan.

Tara Phillips Hi Nathan, As previously discussed, please see... 2012-04-17 11:04:38 AM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-04-17 11:04 AM
Subject: Checklist

Hi Nathan,

As previously discussed, please see below a checklist that I would like you to follow prior to submitting

documents for my review. I would like this checklist to be evergreen so that if you or I identify additional checks that would be useful, we can add them at a later date. Please let me know if any of the items on the list are unclear and I would be happy to discuss. In addition, please let me know if you require training in this regard.

Thank you,

Tara

Checklist:

1) Accuracy

- official names (e.g., organizations, legislation, substances) are spelled correctly and the correct acronym is used

2) Acronyms

- acronyms are used appropriately (for example, the first time a substance name appears, it should be spelled out in full with the acronym directly following in parentheses. The acronym can be used thereafter)

3) Spell Check

- the spell check function (either MS Word or WordPerfect) has been applied to the entire document
- visual check for spelling has been performed by reading through the document

4) Grammar

- there are no run-on sentences
- there is subject-verb agreement

5) Schedule Reference

- use "Schedule to the CDSA" or "Schedule to the NCR" rather than Schedule of



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Designer drug 'bath salts' in Saint John

SAINT JOHN - Bath salts, a devastating, highly-addictive drug, is confirmed to have reached the Saint John region.

Drug analysis tests from **Health Canada** have confirmed that 818 pills seized from a Golden Grove Road home last September contained the substance known as bath salts, said deputy chief Steve Palmer of the Rothesay Regional Police Force.

Bath salts is already common in many U.S. cities, including Bangor, where police have said they respond to around 80 bath salt-related calls a day. The drug, unrelated to bath products, causes euphoria and dangerous hallucinations, similar to methamphetamine.

The Rothesay Regional Police Force issued a warning on Facebook Tuesday, saying that those who experiment with illegal drugs, such as ecstasy, should be cautious because they could be unknowingly ingesting bath salts.

The police agency worked closely with the Saint John Police Force on the September bust, which they described as a "pharmacy" of drugs. They seized a kilogram of marijuana, 29 grams of cocaine, a collection of prescription painkillers and the pills, which were believed to be ecstasy.

The innocent look of the pills was disturbing to investigators.

Pills came in various colours and shapes, including blue hearts, red stars and green cellphones. White and red pills had an imprint of an Air Jordan logo and white pills were stamped with a Virgin logo.

In November, a Bangor police officer spoke to Saint John addictions and criminal justice officials about the dangers of the designer drug.

"We never expected this tidal wave, this tsunami of drugs that came in and stayed," Lieut. Thomas Reagan, a drug recognition expert with the Bangor Police Department, said at the time.

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100



re: MDPV NOI
Nathan Isotalo to: Tara Phillips

2012-04-18 10:53 AM

Hi Tara,

please find attached a draft NOI for MDPV.

Nathan.



NOI MDPV 2012-04-18.doc

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

Notice to interested parties – Proposed amendment to Schedule IV to the Controlled Drugs and Substances Act (CDSA) and the Schedule to Part J to the Food and Drug Regulations (FDR).

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's proposal to add:

- 3,4-methylenedioxypropylamphetamine [MDPV] and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and as sub-item 1(19) to the Schedule to Part J to the FDR.

Recently in Canada there has been an increase in the number of law enforcement and border patrol seizures related to the use, abuse and trafficking of synthetic "bath salt" products containing MDPV, mephedrone and/or methylene. Both mephedrone and methylene are considered to be controlled substances under item 1 of Schedule III to the CDSA. MDPV "bath salt" products are abused for their amphetamine psychostimulant like effects and are available for purchase over the Internet and their recreational use and abuse is now considered widespread across the U.S. and spreading into Canada. "Bath salt" products may be labelled as "not for human consumption". There are currently no legitimate therapeutic, scientific, industrial or commercial uses for synthetic "bath salts" containing MDPV in Canada.

These "bath salt" type synthetic products are not your typical Epsom (magnesium sulphate) bath products despite some similarities in appearance. Canada Border Services Agency (CBSA) has noted an increase in seizures of products found to contain MDPV. Between January 2010 and April 2011, approximately 16 samples tested positive for MDPV while between April 2011 and March 2012, 24 samples tested positive. Two of these samples were from two seizures each of 10 barrels (185 kg) pure MDPV.

Among the seized contraband in a September, 2011 law enforcement seizure in St-John's New Brunswick, were suspicious innocent looking pills. Health Canada's Drug Analysis Service confirmed the presence of "bath salts" in 818 of these pills of various colours and shapes including blue hearts, red stars and green cell phones. White and red pills had an imprint of an Air Jordan logo while white pills were stamped with a Virgin logo. This is evidence that clandestine producers may be experimenting with changing the physical appearance of "bath salt" products possibly to elude law enforcement and border patrol officers as earlier incidents of "bath salt" products involved products that were clear and crystalline like traditional Epsom salts.

The hazards of these products pose significant risks to the health and safety of Canadians. Reported adverse effects of abused bath salt products may include; hypertension, paranoia, delusions, hallucinations, tachycardia, serotonin syndrome, insomnia, psychosis, suicidal thoughts, self-harmful tendencies such as self-mutilation and in some

cases death. There exists a strong abuse and addiction liability potential as indicated from past users experiences. It is often reported that when abuse is stopped that the drug users experience strong cravings compelling them to do self-harm due to the overwhelming psychoactive power of the drug.

Although MDPV is not included in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have adopted controls of their own e.g. the United States, Australia, Denmark, Sweden, United Kingdom.

Including MDPV and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and as sub-item 1(19) to the Schedule to Part J to the FDR would prohibit the following activities with these substances: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. This scheduling will enable law enforcement agencies to take action under the CDSA against suspected illegal activities involving MDPV related substances. This will help to prevent abuse of MDPV from reaching epidemic levels as experienced in other countries.

The publication of this notice begins a 30-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D, 123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca.

CATHY SABISTON
Director General
Controlled Substance and Tobacco Directorate

101



Re: MDPV NOI 
Nathan Isotalo to: Tara Phillips

2012-04-18 11:41 AM

Hi Tara,

I just updated the QP note in case we are asked due to the recent media clipping. I used red line and strikeout.

In this morning's article, 818 pills were identified as bath salts in a September seizure in New Brunswick. No MDPV specific data was mentioned. Perhaps DAS can provide.

Upon editing QP note, I noticed that in the NOI methylene should be methylone. Confusing since methylene is in the chemical name of MDPV.

I replaced the terms in the NOI.

This is the new NOI that you can review now.



NOI MDPV 2012-04-18.doc

Tara Phillips

Thank you Nathan. Please note that if you requir...

2012-04-18 11:07:23 AM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-04-18 11:07 AM
Subject: Re: MDPV NOI

Thank you Nathan. Please note that if you require more time prior to my review, that is no problem. Please confirm.

Thank you,

Tara

Nathan Isotalo

Hi Tara, please find attached a draft NOI for M...

2012-04-18 10:53 AM EDT

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

Notice to interested parties – Proposed amendment to Schedule IV to the *Controlled Drugs and Substances Act* (CDSA) and the Schedule to Part J to the *Food and Drug Regulations* (FDR).

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's proposal to add:

- 3,4-methylenedioxypropylamphetamine [MDPV] and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and as sub-item 1(19) to the Schedule to Part J to the FDR.

Recently in Canada there has been an increase in the number of law enforcement and border patrol seizures related to the use, abuse and trafficking of synthetic "bath salt" products containing MDPV, mephedrone and/or methylone. Both mephedrone and methylone are considered to be controlled substances under item 1 of Schedule III to the CDSA. MDPV "bath salt" products are abused for their amphetamine psychostimulant like effects and are available for purchase over the Internet and their recreational use and abuse is now considered widespread across the U.S. and spreading into Canada. "Bath salt" products may be labelled as "not for human consumption". There are currently no legitimate therapeutic, scientific, industrial or commercial uses for synthetic "bath salts" containing MDPV in Canada.

These "bath salt" type synthetic products are not your typical Epsom (magnesium sulphate) bath products despite some similarities in appearance. Canada Border Services Agency (CBSA) has noted an increase in seizures of products found to contain MDPV. Between January 2010 and April 2011, approximately 16 samples tested positive for MDPV while between April 2011 and March 2012, 24 samples tested positive. Two of these samples were from two seizures each of 10 barrels (185 kg) pure MDPV.

Among the seized contraband in a September, 2011 law enforcement seizure in St-John's New Brunswick, were suspicious innocent looking pills. Health Canada's Drug Analysis Service confirmed the presence of "bath salts" in 818 of these pills of various colours and shapes including blue hearts, red stars and green cell phones. White and red pills had an imprint of an Air Jordan logo while white pills were stamped with a Virgin logo. This is evidence that clandestine producers may be experimenting with changing the physical appearance of "bath salt" products possibly to elude law enforcement and border patrol officers as earlier incidents of "bath salt" products involved products that were clear and crystalline like traditional Epsom salts.

The hazards of these products pose significant risks to the health and safety of Canadians. Reported adverse effects of abused bath salt products may include; hypertension, paranoia, delusions, hallucinations, tachycardia, serotonin syndrome, insomnia, psychosis, suicidal thoughts, self-harmful tendencies such as self-mutilation and in some

cases death. There exists a strong abuse and addiction liability potential as indicated from past users experiences. It is often reported that when abuse is stopped that the drug users experience strong cravings compelling them to do self-harm due to the overwhelming psychoactive power of the drug.

Although MDPV is not included in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have adopted controls of their own e.g. the United States, Australia, Denmark, Sweden, United Kingdom.

Including MDPV and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and as sub-item 1(19) to the Schedule to Part J to the FDR would prohibit the following activities with these substances: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. This scheduling will enable law enforcement agencies to take action under the CDSA against suspected illegal activities involving MDPV related substances. This will help to prevent abuse of MDPV from reaching epidemic levels as experienced in other countries.

The publication of this notice begins a 30-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D, 123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca.

CATHY SABISTON
Director General
Controlled Substance and Tobacco Directorate

103

QUESTION PERIOD NOTE
NOTE POUR LA PÉRIODE DE
QUESTIONS

Date:	April 18, 2012
Classification :	HECS PROTECTED - SESC PROTÉGÉ

SUBJECT - SUJET

English:

MDPV AND MEPHEDRONE IN BATH SALTS

Français:

SYNOPSIS - SOMMAIRE

English:

Recent media articles report that Health Canada Drug Analysis Services has confirmed the presence of MDPV in 818 "bath salt" pills among seized contraband in a September 2011 seizure in St-John's New Brunswick. This adds to recent media attention on the use of "bath salts" as stimulants. In other analyses, "bath salts" may contain a mixture of MDPV (3,4-methylenedioxypropylone), methylone and/or mephedrone. Such products are likely labelled as "bath salts" in order to appear legal. Both methylone and mephedrone are considered controlled substances in Canada, while MDPV is not. Canadian law enforcement and border services are seeing an increasing trend in the incidence of "bath salt" seizures. Health Canada will take appropriate action as needed.

ANTICIPATED QUESTION - QUESTION PRÉVUE

English:

What is the Government doing about MDPV and Mephedrone in bath salts?

Français:

English:

- This government is very concerned about the recent drug analyses and seizures of so-called "bath salts" containing a substance called MDPV.
- Health Canada will be working with law enforcement agencies to determine the most appropriate next steps.
- This Government is committed to controlling substances that produce harm to health and to society when abused.

Français:

s.21(1)(a)

BACKGROUND - CONTEXTE

English:

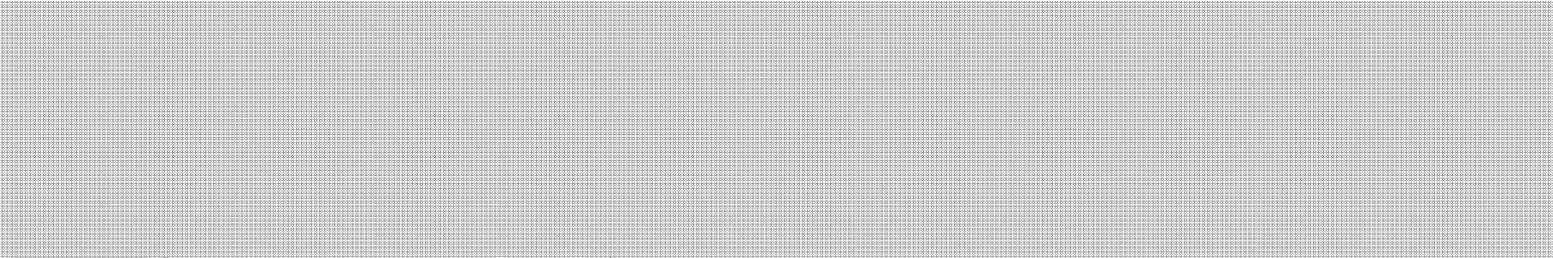
A number of recent media articles in both the United States and Canada have highlighted dangers posed by products labelled and marketed as "bath salts" which are being used as a stimulant. These products are not genuine bath salt products at all, which are typically composed of water soluble mineral salts and are added to water for the purpose of cleansing, softening and/or perfuming the skin.

Preliminary reports indicate that the psychoactive ingredients contained in "bath salt" products may include mephedrone, methylone and/or MDPV.

Mephedrone and methylone are ~~is an~~ analogues of amphetamine and is thus considered to be included in Item 1 of Schedule III to the CDSA. Adverse effects associated with the use of amphetamines can include seizures, cerebral hemorrhage, high fever, coma or death.

MDPV is a central nervous system psychostimulant whose use can cause increased blood pressure and increased heart rate. The use of MDPV has also been associated with panic attacks, anxiety ~~and~~, hallucinations, suicidal thoughts, tendencies and death. MDPV is not regulated as a controlled substance in Canada.

From other analyses, from January 2010 to present, Health Canada's Drug Analysis Service (DAS) has identified MDPV or mephedrone in 332 exhibits of suspected controlled substances seized by law enforcement. 315 of these exhibits were found to contain MDPV alone. Only 17 were found to contain mephedrone.



In the United States, the Drug Enforcement Administration has recently used its emergency scheduling authority to temporarily ban mephedrone, MDPV and methylene. MDPV has also recently been banned in the United Kingdom.

Health Canada will continue to work with law enforcement agencies in determining the most appropriate next steps in addressing the public health and safety risks associated with the use of MDPV.

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

Contact/Personne ressource : Jocelyn Kula/HC-SC/GC/CA	Tel. no./No de tél. 944-0125	Approved by/ Approuvé par Hilary Geller, ADM (HECS/SESC)	Tel. no./No. de tél. 946-6701
	Mobile/ Cellulaire: 613-797-2103	Title/ Titre:	Mobile/ Cellulaire:
Alternate/ Secondaire: Denis Arsenault	Telephone/ Téléphone: 957-6828		
	Mobile/ Cellulaire:		

Date Prepared/Préparé le : 2011-07-21

Prepared by/Préparé par : Angela Doyle **Phone/ No de tél. :** 954-6792

Office/Bureau : CSTD - Office of Controlled Substances

**Date Contact Signed/
Signature de la personne
ressource :** 2012-03-06

Contact Signed - Signé

**D.G. Verification/
Vérification par le D.E. :** Cathy Sabiston

D.G. Approved / Approuvé D.E.

**Date D.G. Verified/
Date vérifié par le D.E. :** 2012-03-06

Programme : Controlled Substances and Tobacco Directorate

**ADM Approved/ Approbation
par le SMA :** Hilary Geller, ADM (HECS/SESC)
(946-6701)

Branch/ Direction générale : HECS/SESC

Department/ Ministère : Health Canada / Santé Canada

104

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Home / News / Local News / Police seize more drugs in raid

Police seize more drugs in raid

By Denis Langlois
Updated 2 months ago

City police believe they are closer to finding the main source of hallucinogenic "bath salts" that have been linked to the hospitalization of at least five people in Owen Sound after a second drug raid in six days.

Det-Sgt. Mark Kielb said 142 grams of what is suspected to be the same designer drug seized during a bust on Jan. 18 was found during a raid Monday night. This time, 10 times more powder was seized by police.

"It was disappointing that we had to encounter more but, on the positive side, we probably got a little closer to the source just because of the significance of the seizure," he said Tuesday in an interview.

Two batches of the powder, both a different colour, were found at a home in the 100 block of 13th St. W.

Samples have been sent off to Health Canada for analysis and more charges could be laid if the substance is found to be illegal, Kielb said.

"What we seized is a raw product. It hasn't been packaged and marketed as bath salts. Until we have it analyzed, we really don't know what we seized," he said.

Police found 14 grams of "bath salts" during the first raid in the 1000 block of 3rd Ave. E. Analysis has revealed that the beige powder contained MDPV, short for methylenedioxypropylamphetamine, a stimulant found in the so-called "bath salts" that have been linked to deaths and suicides in the United States and Europe.

In Owen Sound, police believe the drug caused five men, seen by doctors at the city's emergency department, to experience similar symptoms of extreme paranoia, vivid hallucinations and thoughts of suicide.

Kielb said police are still trying to determine if MDPV is illegal in Canada and if officers can lay charges related to its sale or possession.



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So far city police believe it is not a regulated substance, but say they plan to continue looking into it.

"Investigators have received conflicting information as to whether or not this drug is regulated in Canada and are continuing to make inquiries," Kielb said in a police statement.

The RCMP says drugs imported, packaged and sold as "bath salts," and seized by police have been found to contain several synthetic substances, including MDPV and mephedrone.

Sgt. Julie Gagnon, an RCMP media relations officer, said mephedrone is regulated in Canada under the Controlled Drugs and Substances Act but MDPV is not.

Health Canada, meanwhile, says MDPV is not approved for sale in Canada and is a controlled substance, as it is "related" to mephedrone. *→ Not true → not in C. S.*

Six officers from the Owen Sound police department's drug unit, criminal investigation branch and High Enforcement Action Team used a warrant to raid a home Monday night.

Along with the suspected "bath salts," police also seized a small amount of marijuana and codeine, along with a .22 calibre rifle, ammunition and drug trafficking paraphernalia.

The male resident was not home at the time of the search and police are seeking a warrant for his arrest. He faces charges of possession of marijuana, possession of codeine, unauthorized possession of a firearm, careless storage of a firearm and unauthorized possession of ammunition.

In the meantime, police have issued a warning to stay away from "bath salts," saying it is dangerous.

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105



re: triage
Nathan Isotalo to: Tara Phillips

2012-04-23 10:42 AM

Good morning, Tara,

please find below the MDPV triage for internal approval. Nathan.



MDPV Triage 2012-04-23.rtf



106

s.21(1)(a)
s.21(1)(b)

Triage Statement Form

Section I: Overview

Security classification
Protected B

Date received by RAS: April 2012

Title of the Regulatory Proposal: Regulation Amending Schedule IV to the CDSA and Schedule to Part J of the FDR to include MDPV

Sponsoring Regulatory Organization: Health Canada

Statutory Authority: *Controlled Drugs and Substances Act*

Approximate date of submission of regulatory proposal to PCO-OIC: [REDACTED]

Issue

In North America, over the past couple of years, reports of a new designer drug typically referred to as “bath salts” has been steadily increasing. In Canada, marginal slight increases in seizures do not yet indicate widespread usage of “bath salts” in the general population. These synthetics are not traditional epsom salts¹. Although they may be similar in physical appearance “bath salts” have been found to contain mephedrone, methylone² and/or 3,4-methylenedioxypropylvalerone (MDPV). Illicit products of synthetic “bath salts” may be purchased over the Internet or in some alternative lifestyle stores in small packages labelled as “bath salts” or “plant food”. There are no known legitimate therapeutic, scientific, industrial or commercial uses for these synthetic “bath salts” or MDPV in Canada.

The Canadian Border Services Agency (CBSA) has noted an increase in the amount of samples found to contain MDPV. Between January 2010 and April 2011 approximately 16 samples tested positive for MDPV while between April 2011 and March 2012, 24 samples tested positive. Two of these samples were from two seizures of 10 barrels each of 185 kg pure MDPV.

MDPV belongs to a group of substances called phenylethyamines which are analogues of amphetamines and 3,4-methylenedioxymethamphetamine (MDMA). MDPV has some chemical similarities to the amphetamine cathinone and other controlled substances such as phenmetrazine and pyrovalerone. Currently, MDPV is not a controlled substance under the *Controlled Drugs and Substances Act* (CDSA).

¹ Epsom salts are consumer products of a naturally occurring mineral known as hydrated magnesium sulphate. They are used for their therapeutic benefits including skin exfoliation, bathing relaxation and reduced swelling. They may be purchased at your local supermarket or drugstore. In Canada, such products fall under the definition of consumer product of the *Canada Consumer Product Safety Act* (CCPSA).

² In Canada, both mephedrone and methylone are controlled substances under item 1 of Schedule III to the CDSA.

Illicit products of synthetic “bath salts” may be abused by various exposure routes and administrative means such as oral ingestion, nasal inhalation or injection into the blood stream or muscle. Reported adverse effects include: hypertension, paranoia, delusions, hallucinations, tachycardia, serotonin syndrome, insomnia, psychosis, suicidal thoughts, self-harmful tendencies such as self-mutilation and death. It has been reported that when abuse is stopped that drug users experience intense cravings. This is due to their physical dependence on the drug. Tolerance thresholds are often exceeded so that more drug is needed to create the psychostimulant “high”.

As there exist significant risks to both personal and public safety and security from the availability of MDPV, a *Notice to Interested Parties* will be published in *Canada Gazette*, Part I seeking stakeholder input on Health Canada’s proposal to add MDPV to Schedule IV to the CDSA and to the Schedule to Part J of the *Food and Drug Regulations* (FDR) to the CDSA.

Internationally, MDPV is not listed on any of the Schedules to the UN Drug Conventions and consequently not listed on either the yellow or green lists of the International Narcotic Control Board (INCB). MDPV is however, controlled to various degrees in several different countries such as the United States, Australia, the United Kingdom, Denmark, Sweden and Ireland. In the United States of America (USA/US), the US Drug Enforcement Administration (DEA) has temporarily added MDPV, mephedrone and methylene to Schedule I to the US *Controlled Substances Act* (CSA) to address the epidemic widespread abuse of MDPV “bath salts” across the country. MDPV is also controlled under some State laws including those of Louisiana, Florida, Kentucky, New Jersey, Tennessee, Maine and Ohio.

Objectives

Scheduling MDPV under CDSA would prohibit all activities, e.g., possession, importation, and exportation, involving MDPV. The CDSA sets out penalties for illegal activities involving substances listed in its Schedules and the Regulations under the CDSA establish tight controls on the movement of regulated substances with a view to reducing abuse and diversion to the illicit market. As such, scheduling will enable law enforcement to respond to illegal activities. The ultimate goal of this regulatory proposal is to reduce the risks to the health and safety of Canadians posed by the availability of MDPV. Part J of the FDR under the CDSA lists restricted drugs namely, those substances that could possibly be used for future legitimate scientific research activities in Canada, if required.

Description

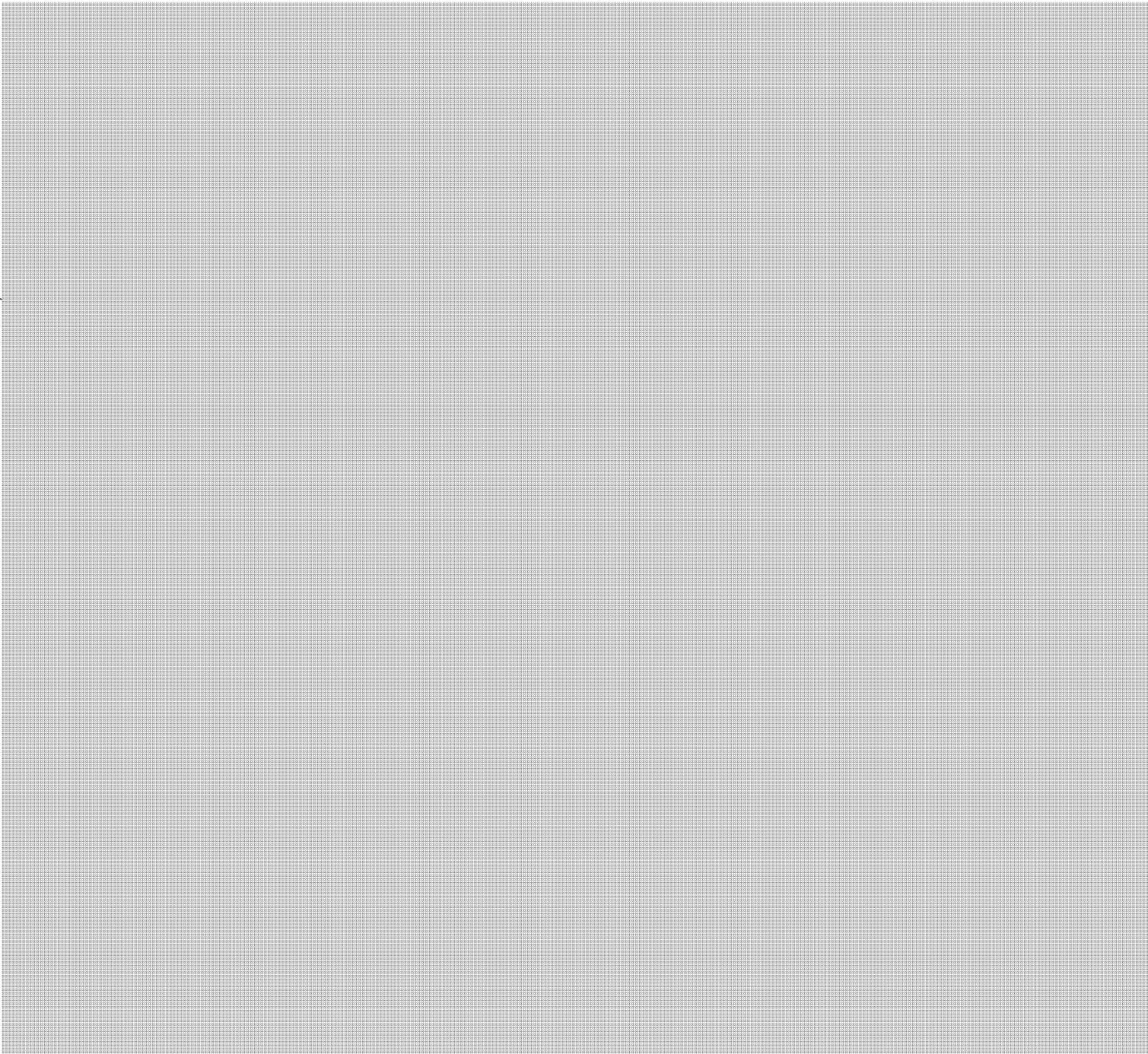
Health Canada proposes to add MDPV, its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule IV to the CDSA and to the Schedule to Part J of the FDR to the CDSA.

Page(s) 000577 to\à 000582

**Is(Are) exempted pursuant to section(s)
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**



Departmental signoff (Director): _____

Date _____

s.21(1)(a)

s.21(1)(b)

Mrs. Johanne Beaulieu
Director, Office of Controlled Substances
Controlled Substances and Tobacco Directorate, HECS Branch, Health Canada

Name and address of departmental contact person:

Mr. Nathan Isotalo
123 Slater St., A304
Ottawa, ON K1A 0K9
Tel. (613) 941-1511

RAS signoff (analyst):

Date: _____

The regulatory organization should send two signed copies of the final Triage Statement to RAS. RAS will then sign the two Triage Statements and return one copy to the regulatory organization.

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Article

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BYLINE: April Cunningham Telegraph-Journal
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WORD COUNT: 563
CIRCULATION: 33080

Status of 'bath salts' remains unknown

SAINT JOHN - It's unclear how long it could take for the main ingredient in bath salts, a new synthetic drug now confirmed to have hit the Saint John region, to become illegal.

Health Canada is considering assessing the active drug, MDPV, to be added to the list of controlled substances under federal law, according to a statement from the department.

"**Health Canada** is in contact with the RCMP and law enforcement agencies on this issue," said spokesman Gary Holub in an email.

He said the department would consider adding the drug under the Controlled Drugs and Substances Act "should intelligence suggest that the availability of MDPV and/or 'bath salt' products in Canada warrant further action."

The department could not provide a timeline on how long that process might take.

Health Canada considers several factors when determining whether a drug should be added to the list of controlled substances, including the overall risk to public health, chemical and pharmacological similarity to other regulated substances, legitimate use of the substance, and potential for abuse and risk of addiction.

"MDPV is not a controlled substance, but the department will be working with law enforcement agencies to determine the most appropriate steps to take to ensure that MDPV is controlled in Canada," he said.

109

Fw: URGENT QP MO REQUESTS - HECSB

Tara Phillips to: Nathan Isotalo

2012-04-25 09:42 AM

Hi Nathan - can you please call my cell phone to discuss?

s.19(1)

Tara

Jocelyn Kula

----- Original Message -----

From: Jocelyn Kula

Sent: 2012-04-25 09:40 AM EDT

To: SoniaH Lindblad1; Johanne Beaulieu; Patricia Rapold

Cc: Arafo Talane; Tara Phillips; Nathan Isotalo

Subject: Re: URGENT QP MO REQUESTS - HECSB

Sorry Sonia, we are in retreat today and I just saw this.

We are on it.

JK

Sent by blackberry

SoniaH Lindblad1

Someone needs to let me know if you've see...

2012-04-25 09:37 AM EDT

From:

SoniaH Lindblad1

To:

Johanne Beaulieu; Patricia Rapold

Cc:

Arafo Talane; Jocelyn Kula

Date:

2012-04-25 09:37 AM EDT

Subject:

Fw: URGENT QP MO REQUESTS - HECSB

Someone needs to let me know if you've seen this request. and are actioning it..DUE BY 10AM this morning.

Sonia Lindblad

Executive Assistant to the DG/Adjointe exécutive au DG

Controlled Substances and Tobacco Control Directorate

Health Canada/Santé Canada

Tel: 613-946-9316 Fax: 613-954-2288

----- Forwarded by SoniaH Lindblad1/HC-SC/GC/CA on 2012-04-25 09:36 AM -----

From:

SoniaH Lindblad1/HC-SC/GC/CA

To:

Johanne Beaulieu/HC-SC/GC/CA@HWC, Mélanie Séguin/HC-SC/GC/CA@HWC, Patricia Rapold/HC-SC/GC/CA@HWC, Arafo Talane/HC-SC/GC/CA@HWC

Date:

2012-04-25 09:23 AM

Subject:

URGENT QP MO REQUESTS - HECSB

Please update the attached QP with the attached article for 10am this morning.

thanks,

 Here's the bathsalts note

1) an updated note on bath salts -

http://206.75.155.80/health_ca/ashow.asp?U=120424/nbtj/1204240E.htm&D=1462&A=38

Nadia Biasotto
Office of the Assistant Deputy Minister / Bureau du sous-ministre adjoint
Healthy Environments and Consumer Safety Branch / Direction Générale, Santé
Environnementale et Sécurité des Consommateurs
Executive Services / Services Exécutifs

Health Canada / Santé Canada

Tel | Tél : (613) 960-4700
Fax | Téléc : (613) 946-6666
E-mail | Courriel : nadia.biasotto@hc-sc.gc.ca

SoniaH Lindblad1	Hi Nadia, marihuana cups is either RCMP or a J...	2012-04-25 09:17:34 AM
Nadia Biasotto	Sonia please see request below. Please confir...	2012-04-25 09:12:26 AM

|||



Re: Fw: MDPV QP

Johanne Beaulieu to: Sherstone, Andria, Lindblad1, SoniaH
Cc: "Kula, Jocelyn", "Isotalo, Nathan", "Phillips, Tara"

2012-04-25 10:17 AM

Good Day!

This is approved.

Johanne

Nathan Isotalo

Date: April 25, 2012 QUESTION PERIOD NOTE

2012-04-25 10:11 AM EDT

From: Nathan Isotalo
To: Jocelyn Kula
Cc: Johanne Beaulieu
Date: 2012-04-25 10:11 AM EDT
Subject: Re: Fw: MDPV QP

Date: April 25, 2012

QUESTION PERIOD NOTE

NOTE POUR LA PÉRIODE DE QUESTIONS Classification: HECS
PROTECTED - SESC PROTÉGÉ

MDPV AND MEPHEDRONE IN BATH SALTS

SYNOPSIS

Recent media articles report that Health Canada Drug Analysis Services has confirmed the presence of MDPV in 818 "bath salt" pills among seized contraband in a September 2011 seizure in St-John's New Brunswick. On 2012-04-24, the New Brunswick Telegraph reported additional findings surrounding the previous seizure and efforts to control MDPV in Canada. This adds to recent media attention on the use of "bath salts" as stimulants. In other analyses, "bath salts" may contain a mixture of MDPV (3,4-methylenedioxypropylone), methylone and/or mephedrone. Such products are likely labelled as "bath salts" in order to appear legal. Both methylone and mephedrone are considered controlled substances in Canada, while MDPV is not. Canadian law enforcement and border services are seeing an increasing trend in the incidence of "bath salt" seizures. Health Canada will take appropriate action as needed.

ANTICIPATED QUESTION

What is the Government doing about MDPV and Mephedrone in bath salts?

This government is very concerned about the recent drug analyses and seizures of so-called "bath salts" containing a substance called MDPV.

Health Canada will be working with law enforcement agencies to determine the most appropriate next steps.

This Government is committed to controlling substances that produce harm to health and to society when abused.

BACKGROUND

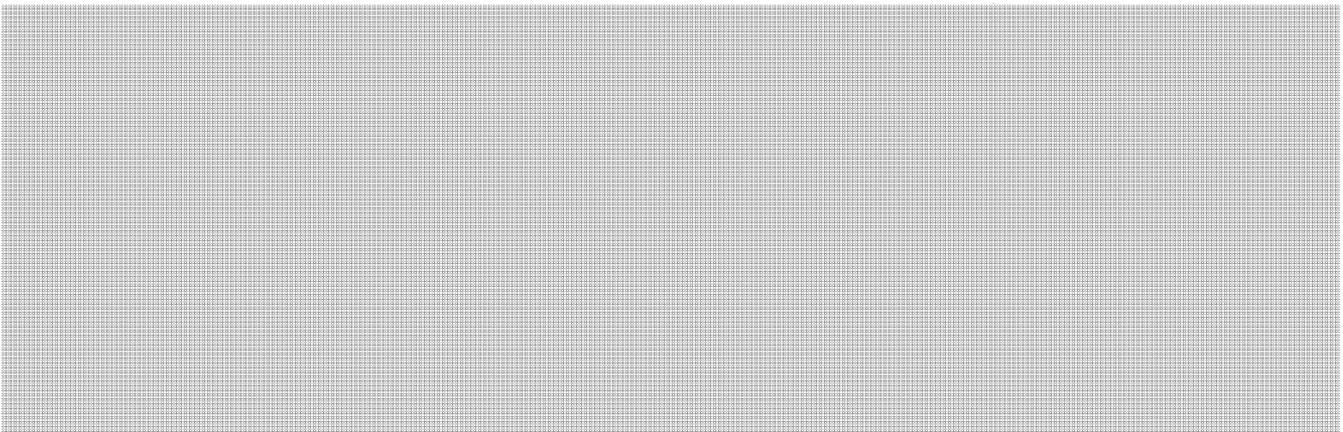
A number of recent media articles in both the United States and Canada have highlighted dangers posed by products labelled and marketed as "bath salts" which are being used as a stimulant. These products are not genuine bath salt products at all, which are typically composed of water soluble mineral salts and are added to water for the purpose of cleansing, softening and/or perfuming the skin.

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In the United States, the Drug Enforcement Administration has recently used its emergency scheduling authority to temporarily ban mephedrone, MDPV and methyone. MDPV has also recently been banned in the United Kingdom.

Health Canada will continue to work with law enforcement agencies in determining the most

appropriate next steps in addressing the public health and safety risks associated with the use of
MDPV.

Jocelyn Kula The link is attached. Nathan pls cut and paste t... 2012-04-25 10:00:59 AM

From: Jocelyn Kula/HC-SC/GC/CA
To: "Johanne Beaulieu" <johanne.beaulieu@hc-sc.gc.ca>
Cc: "Nathan Isotalo" <nathan.isotalo@hc-sc.gc.ca>
Date: 2012-04-25 10:00 AM
Subject: Fw: MDPV QP

The link is attached.
Nathan pls cut and paste text so Johanne can read on her BB.

JK

Sent by blackberry
Nathan Isotalo

----- Original Message -----

From: Nathan Isotalo
Sent: 2012-04-25 09:58 AM EDT
To: Jocelyn Kula
Cc: Tara Phillips; Nathan Isotalo
Subject: re: MDPV QP

Hi Jocelyn,

as requested by Tara, please find a link to the bath salt (MDPV) QP note.

Nathan.



112



Fw: MO Request regarding Bath Salts
Jocelyn Kula to: Tara Phillips, Nathan Isotalo

2012-04-25 05:28 PM

for the file pls

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224
---- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2012-04-25 05:27 PM ----

From: Louise Bertrand/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC, Johanne Beaulieu/HC-SC/GC/CA@HWC
Cc: Cathy A Sabiston/HC-SC/GC/CA@HWC, Andria Sherstone/HC-SC/GC/CA@HWC, CSTD-OCS-DO
Date: 2012-04-25 12:05 PM
Subject: Fw: MO Request regarding Bath Salts

fyi - sent to ADMO... HUGE THANKS!!!

---- Forwarded by Louise Bertrand/HC-SC/GC/CA on 2012-04-25 12:04 PM ----

From: Louise Bertrand/HC-SC/GC/CA
To: Ian Hobler/HC-SC/GC/CA@HWC
Date: 2012-04-25 12:03 PM
Subject: Fw: MO Request regarding Bath Salts

Three main areas of activity for MDPV:

1. We are currently working on our scheduling assessment for MDPV, which includes an external contract for the assessment of pharmacology data (completion Spring 2012).
2. Triage questionnaire in final stages of development. [REDACTED]
3. Notice of Intent to Interested Parties in early stages of development.

Let me know if you need anything else.

Louise Bertrand Hi, ADMO just informed me that MO would lik... 2012-04-25 11:49 AM EDT

From: Louise Bertrand
To: Johanne Beaulieu
Cc: Cathy A Sabiston; Andria Sherstone; CSTD-OCS-DO; Jocelyn Kula
Date: 2012-04-25 11:49 AM EDT
Subject: MO Request regarding Bath Salts

Hi,
ADMO just informed me that MO would like to know what CSTD activities are on-going with regards to the assessment of "Bath Salts"/MDPV (e.g. analysis steps, meetings, etc...).

000591

MO is briefing Minister in the next few minutes and wants this info now.

Thanks,

Louise Bertrand

DGO Advisor | Conseillère

Controlled Substances and Tobacco Directorate | Direction des substances contrôlées et de la lutte au
tabagisme

Health Canada | Santé Canada

(613) 957-2867

113



re: legal opinion?

Nathan Isotalo to: Tara Phillips

2012-04-26 12:14 PM

Hi Tara,

as follow up to your enquiry, and as a caveat to MDPV related drafts, MDPV was recommended for Schedule IV as pyrovalerone and phenmetrazine are Schedule IV and MDPV shares structural similarities to these compounds as per status decision. When drafting I had to make a proposal one way or the other.

We may need to seek a legal opinion from Norma Won as to where in the Schedules to the CDSA it is best to schedule MDPV given risk to public health and safety and which type of penalties should be adopted. Consequently, this could change on which Schedule MDPV should be added to.

Nathan.



Re: Question on MDPV File 
Nathan Isotalo to: Tara Phillips

2012-04-26 12:37 PM

Hi Tara, yes we an alert from the RCMP. Nathan.

Tara Phillips Hi Nathan, Do we have any references on the fil... 2012-04-26 12:30:37 PM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-04-26 12:30 PM
Subject: Question on MDPV File

Hi Nathan,

Do we have any references on the file to increasing seizures by law enforcement? I would assume this would be in the form of correspondence with police or with DAS lab but perhaps other documentation may have it as well.

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca



Re: For Action: Footnote statement related to rescheduling of amphetamines

Nathan Isotalo to: Tara Phillips

2012-04-26 01:56 PM

Mephedrone and methylone are considered falling under Schedule III to the CDSA as they are analogues of controlled substances already listed under Schedule III to the CDSA.

~~Mephedrone is an analogue of both 4-methylmethamphetamine and methcathinone which are listed under items 1 and 21 of Schedule III to the CDSA respectively. Similarly, methylone is an analogue of MDMA (Ecstasy) and methcathinone which are also listed under items 1 and 21 of Schedule III to the CDSA.~~

MDPV is not currently considered to fall under the Schedules to the CDSA despite MDPV sharing a basic structural element with several controlled substances including: cathinone, methcathinone, diethylpropion, phenmetrazine and pyrovalerone.

Tara Phillips

Hi Nathan, Could you please send me a footnot...

2012-04-26 12:44:01 PM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-04-26 12:44 PM
Subject: For Action: Footnote statement related to rescheduling of amphetamines

Hi Nathan,

Could you please send me a footnote statement for this statement in the Notice:

Mephedrone and methylone are analogues of amphetamine and is thus considered to be included in Item 1 of Schedule III to the CDSA.

to capture the notion that the Safe Streets and Communities Act reschedules these substances but that the coming into force date is not yet set.

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

116



re: request
Nathan Isotalo to: Tara Phillips

2012-04-26 02:28 PM

Hi Tara,

fyi- was aware of Bill C-10 but not its contents. Here is a footnote that you can use:

"Under the new *Safe Streets and Communities Act* (Bill C-10), GHB, flunitrazepam and amphetamine drugs will be moved from Schedule III to Schedule I to the CDSA.

This will result in higher maximum penalties for illegal activities involving these drugs. As both mephedrone and methylone have been recommended to be included in item 1 to Schedule III to the CDSA, upon Royal Assent, mephedrone and methylone may be considered as falling under Schedule I to the CDSA."

117



For Your Review: Draft Notice on MDPV
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-04-26 03:14 PM

Hi Jocelyn,

Please find attached, for your review, a draft *Notice to interested parties* regarding the proposal to control MDPV under the CDSA.



NOI MDPV 2012-04-26.doc

Further to yesterday's discussion, Nathan and I will revise the workplan and submit to you for review later today or tomorrow.

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

110



For Your Review: Revised MDPV Workplan
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-04-27 10:23 AM

Hi Jocelyn,

Please find attached, for your review, a revised workplan for the scheduling of MDPV.

This version has the same finish line as the previous one, which is publication in CGII in December 2012.
I tweaked the earlier parts a little bit to reflect the current reality but overall no major changes.



DRAFT MDPV WorkPlan Apr 26, 2012.doc

Thank you,

Tara

WORKPLAN: Scheduling of MDPV under the Controlled Drugs and Substances Act

Task/Activity		Target Date	Lead	Status
TRIAGE STATEMENT				
1	Draft triage statement	May 4, 2012	RPD	Ongoing
2	Consult with Treasury Board Secretariat	May 11, 2012	RPD, TBS	Ongoing
3	Obtain Director approval of triage statement	May 18, 2012	RPD, DO	
4	Obtain TBS approval of triage statement	May 25, 2012	RPD, DGO	
NOTICE TO INTERESTED PARTIES (Notice) - for publication in Canada Gazette, Part I				
1	Draft Notice	April 27, 2012	RPD	Ongoing
2	Obtain Director approval of Notice	April 30, 2012	RPD, DO	
3	Obtain DG, CSTD approval of Notice	May 4, 2012	RPD, DGO	
4	Brief senior management (ADM/DM) on Notice, as required	May 11, 2012	RPD, DGO, ADMO	
5	Submission to Canada Gazette Directorate (6 working days in advance of publication date)	May 17, 2012	RPD, Canada Gazette Directorate	
6	Publication in <i>Canada Gazette</i> , Part I	May 26, 2012	Canada Gazette Directorate	
7	60-day comment period ends (Duration of comment period to be confirmed – 30, 60 or 75 days)	July 25, 2012	RPD	
8	Review and analysis of comments received	August 3, 2012	RPD	

ISSUE ANALYSIS SUMMARY

1	Research & Analysis	May 25, 2012	RPD & ORS	Ongoing
2	Draft Issue Analysis Summary	June 8, 2012	RPD	Ongoing
3	Controlled Substances Scheduling Working Group	July Meeting	RPD & CSSWG	
4	Obtain Director, OCS approval of Issue Analysis Summary	July 27, 2012	RPD, DO	

REGULATORY PROPOSAL

Note: Provided that no legitimate industry is identified via *Notice to interested parties*, there will be no administrative burden or compliance burden associated with proposal. Therefore, Regulatory Cost Calculator results will not be required.

I. Preparation of Drafting Instructions

1	Prepare drafting instructions	July 25, 2012	RPD	
3	Legal Services Review of drafting instructions	July 31, 2012	LSU	
4	Translate drafting instructions	August 1, 2012	RPD	
5	Obtain Director, OCS approval of drafting instructions	August 2, 2012	RPD, DO	
6	Obtain DG, CSTD approval of drafting instructions	August 7, 2012	RPD, DGO	
7	Submit drafting instructions to Department of Justice Drafting Service	August 8, 2012	RPD	

**s.21(1)(a)
s.21(1)(b)**

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Page(s) 000601 to\à 000601

**Is(Are) exempted pursuant to section(s)
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**

121



For Your Review: Revised Notice on MDPV
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-04-27 11:20 AM

Hi Jocelyn,

Further to your comments, a revised Notice is attached, for your review.



NOI MDPV 2012-04-27.doc

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

*Notice to interested parties – Proposed amendment to Schedule III to the Controlled
Drugs and Substances Act*

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's intent to add 3,4-methylenedioxypropylamphetamine (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule III to the *Controlled Drugs and Substances Act* (CDSA).

This proposed action is in response to recent increases in law enforcement and border seizures of products labelled as "bath salts". Such products are not genuine bath salt products intended for softening/cleansing the skin, but are in fact a synthetic drug with stimulant properties. MDPV poses a potential risk to the health and safety of Canadians since its use can cause increased blood pressure and increased heart rate and has also been associated with panic attacks, anxiety, hallucinations, suicidal thoughts and death.

While the extent of their use in Canada is unknown, "bath salts" products are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky". "Bath salts" products have also been found to contain mephedrone and methylone, which are analogues of amphetamine and thus considered to be included in Schedule III to the CDSA.

Although MDPV is not listed in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have already elected to regulate it as a controlled substance, including the United States, Australia, Denmark, Sweden and the United Kingdom.

Including MDPV in Schedule III to the CDSA would prohibit the following activities with this substance: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The scheduling of MDPV will also ensure law enforcements can take action against all suspected illegal activities involving MDPV.

Health Canada is not aware of any legitimate medical, scientific or industrial applications for MDPV and is therefore not intending to regulate MDPV in accordance with existing regulatory schemes under the CDSA.

The publication of this notice begins a 60-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D, 123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email

at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. In particular, parties involved in legitimate activities involving MDPV are encouraged to respond to inform Health Canada's decision with respect to regulation of MDPV under the CDSA.

CATHY SABISTON

Director General

Controlled Substance and Tobacco Directorate

122



For Action: Review of Draft MDPV Assessment

Tara Phillips to: Nathan Isotalo

2012-04-30 04:59 PM

History: This message has been replied to.

Hi Nathan,

Please review the attached document and provide written comments to me by close of business tomorrow, Tuesday, May 1st. If this deadline does not provide you with adequate time, please let me know at your earliest convenience and we can discuss.

Please use the checklist that I sent to you on April 17, 2012, to assess your written comments prior to submitting them to me.

Thank you,

Tara

----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2012-04-30 01:48 PM -----

From: Erin Rutherford/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-04-30 01:43 PM
Subject: Draft MDPV assessment for comments

Attached please find a draft MDPV assessment for your review and comments.



MDPV Assessment DRAFT.doc

I would appreciate if you could provide me with any comments prior to COB Wednesday.

Regards

Erin Rutherford

Manager/Gestionnaire
Drugs and Alcohol Research/Recherche, drogues et alcool
Office of Research and Surveillance / Bureau de la recherche et de la surveillance
Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au tabagisme
Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada / Santé Canada

123 Slater, MacDonald Building
Room A616 Address Locator: AL 3506 D
Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210
Fax: (613) 952-5188
E-mail: erin.rutherford@hc-sc.gc.ca

000605

**3,4-Methylenedioxypropylvalerone (MDPV) Abuse Liability and Dependence
Potential Assessment**

Prepared by Vlad Kushnir, MSc
April 30, 2012

3,4-Methylenedioxypropylone (MDPV) Abuse Liability and Dependence Potential Assessment

Background

The synthetic cathinone 3,4-Methylenedioxypropylone, also known as MDPV, is a designer drug that is used for its cocaine and amphetamine-like psychoactive effects. First synthesized and patented by Boehringer Ingelheim in 1969,¹ it has only recently gained exposure among recreational drug users. It is one of a number synthetic cathinones that are derivatives of the vegetable cathinone, a naturally occurring beta-ketone amphetamine analogue found in the leaves of *Catha edulis* (khat). Considered as “legal highs”, synthetic cathinones are generally sold as “bath salts” or “plant food” and labelled “not for human consumption” to circumvent regulatory control and drug abuse legislation. MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities. The substance does not have any known medical uses and is an analogue of the compound propylone (a Schedule V controlled substance).

Chemistry

Chemical Structure

The compound 3,4-Methylenedioxypropylone (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5yl)-2-pyrrolidin-1-yl-pentan-1-one) is a pyrrolidine derivative of the synthetic cathinone propylone, differing in the presence of a 3,4-methylenedioxy group linked to the aromatic ring.¹ Its molecular formula is C₁₆H₂₁NO₃ and has a molecular weight of 275.34284 g/mol; Chemical Abstract Service Number 687603-66-3. MDPV is a solid at room temperature and has a melting point of 209.3 °C and a boiling point of 476 °C. It is available as an amorphous solid or crystalline powder that varies in colour, depending on composition and added impurities. In the free base form it is brown or yellowish green, whereas as a hydrochloride salt it is white in appearance.

Pharmacology

Biotransformation

The metabolism of MDPV has been evaluated only *in vitro* in two studies. Examination of MDPV metabolism in human liver cells has prompted the proposal of a metabolic pathway that involves first, the opening of the methylenedioxy ring, followed by demethylation that gives rise to a catechol ring, which is in turn methylated by catecholmethyltransferase.² The aromatic pyrrolidine ring and side chain are subsequently hydroxylated, followed by oxidation to the corresponding lactam, as well as ring opening to the corresponding carboxylic acid. It was documented that the demethylation step of the Phase I metabolism, in particular, is catalyzed

through CYP450 isozymes 2C19, 2D6 and 1A2.³ Approximately 80% of MDPV remains unmetabolized, 10% is metabolized into cetechol pyrovalerone, and 7% is metabolized into methylcatechol pyrovalerone. The high percentage of the parent compound was postulated to remain as a result of very high concentrations of MDPV added to liver microsome samples. Nevertheless, it was determined that the main metabolites further undergo Phase II glucoronidation and sulfation transformations to allow for renal excretion.²

Elimination

The excretion profile of MDPV and its metabolites has not been studied in animals or humans. However, several reports have documented MDPV concentrations in urine samples obtained from patients presenting to hospital and poison centres, as well as opioid dependent patients undergoing opioid substitution treatment. MDPV concentrations in urine have been noted to range from 0.034 – 3.9 mg/L in those cases.⁴⁻⁶ While anecdotal reports indicate that users ingest anywhere between 5 – 30mg of MDPV per single session,⁶⁻⁸ variable dose intake among users and undocumented time since ingestion prohibit from determining the MDPV elimination half-life and concentration of excreted metabolites.

Pharmacological Mechanism of Action

The exact mechanism of action of MDPV has not been fully elucidated, with only a handful of studies investigating its neurobiological effects. *In-vitro*, MDPV has demonstrated to act as a potent dopamine ($IC_{50} = 52.0 \pm 20$ nM) and norepinephrine ($IC_{50} = 28.3 \pm 8.1$ nM) reuptake inhibitor, exhibiting dopamine and norepinephrine reuptake inhibition 9 and 13 times greater than cocaine, respectively. In contrast, inhibition of serotonin reuptake was found to be markedly less pronounced ($IC_{50} = 2780 \pm 590$ nM), a finding that reflected in the reduced binding affinity for the serotonergic transporter.⁹ Microdialysis studies in freely moving mice supported the *in-vitro* findings, showing that 60 minutes following oral administration of MDPV, extracellular striatum dopamine content was 2.1 times higher in the experimental group compared to those in the control group. While substantial, MDPV induced increases in dopamine levels, however, were milder than those produced by the amphetamine-like stimulants methamphetamine and methylenedioxymethamphetamine (MDMA). Further, serotonin concentrations were not significantly influenced by MDPV administration.^{10, 11}

Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. MDPV binding affinities at the dopamine transporter ($K_i = 21.4 \pm 4.6$ nM) and norepinephrine transporter ($K_i = 195 \pm 26$ nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively. Binding affinity for the serotonin transporter was considerably lower ($K_i = 3770 \pm 560$ nM), indicating that MDPV is relatively inactive at this site.⁹

Human Toxicology

At present, a toxicological profile for MDPV, including a dose-response relationship and the median lethal dose (LD₅₀), has not yet been established. Primary indication of MDPV toxicity in the scientific community has developed from case reports documenting individuals presenting to hospital emergency departments after intake of "bath salts". The most common symptoms of acute toxicity involve those associated with cardiovascular, neurological, and psychopathological function. Specifically, they include: tachycardia, chest pain, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, delusions, auditory and visual hallucinations, paranoid psychosis, agitation, aggression, anxiety, panic attacks, insomnia, memory loss, hyperthermia, rhabdomyolysis, abdominal pain, decreased appetite, vomiting, and kidney dysfunction.^{4, 12-17} Some effects such as sleeping difficulties, anxiety and agitation have been reported to persist for more than one day following ingestion,¹³ while others have been suggested to continue for as long as a week.¹⁵ Several cases of drug-induced delirium and even death have also been noted, where MDPV was the sole intoxicant.^{14, 17} Most commonly, however, as MDPV is co-ingested with other substances, including benzodiazepines, amphetamines, cannabis, and ethanol,^{5, 18} it is unclear whether the list of acute toxic effects is purely a result of MDPV or a combination of drug-drug interactions.

Evidence of Abuse Liability

Animal or human laboratory studies on abuse liability of MDPV have not been carried out. Specifically, the most common approaches used to investigate abuse potential of drugs in animals, namely, self-administration tests, conditioned place preference, drug discrimination, and psychomotor tests are not documented in the scientific literature. Similarly, abuse liability trials in recreational drug users using double blind, randomized, double dummy, placebo or positive comparator controlled, or crossover designs have not been conducted. Only one study has made an inference to MDPV being liable to abuse. Through the use of the gas chromatography-mass spectrometry procedure to detect MDPV and other substances in urine of opioid-dependent patients undergoing opioid substitution treatment, the authors suggested that MDPV is mainly used a "non-detectable" substitute for amphetamine primarily to increase concentration among users. Moreover, they emphasized that the inability to detect MDPV through conventional immunoassay drug screenings is a notable factor that may contribute to the drug's misuse.⁶

The numerous case reports of acute MDPV intoxication highlighted in the scientific literature may be in their own respect, an indirect indication that the drug may possess abuse potential. Among recreational drug users, MDPV may be gaining popularity specifically for its anecdotal desired subjective effects. Synthesizing internet information on the effects of MDPV, one review has noted that specifically at low doses (undefined), MDPV is used to increase concentration, the capacity to work, and sexual performance. Other desired psychotomimetic effects include increased sociability, energy, limited euphoria, and mild empathogenic effects.⁷

Evidence of Physical Dependence

Behavioural animal data on the reinforcing and physical dependence-producing effects of MDPV is not available. Clinical trials on MDPV abuse liability have also not been conducted, therefore scientific evidence of tolerance or withdrawal, which is critical to the definition of physical dependence, has not been observed. Although one literature source cited the “development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV”,⁷ these drug-related effects could not be confirmed.

Evidence of possible physical dependence and tolerance building effects is indirect and can only be gleaned from case studies and unverified internet information reported by users. Penders and Gestring¹⁴ reported of a woman admitted to the psychiatric unit of a community hospital by way of an involuntary commitment initiated by her husband. The individual experienced fearful hallucinations of a home invasion that precipitated following daily use of MDPV for 2 weeks prior to admission. It is possible to infer that repeated and perhaps uncontrollable use of the drug is suggestive of physical dependence-like effects, however, this conclusion is highly speculative. Indication of possible tolerance is based on internet discussions documenting common redosing in a single session as well as using doses of over 200mg.⁷ Although MDPV is reported to have a short duration of action, use of doses well over 6 times the typical 5 to 30 mg used in a single ingestion, suggests that users may develop tolerance to the drug's effects and thus possible physical dependence.

Conclusions

The abuse potential assessment of a drug should be based on a composite analysis of chemistry, pharmacology, clinical data, health risks that the drug presents, as well as ease of access to the drug and administration. The limited pharmacological data suggests that MDPV is similar to other synthetic cathinones, inhibiting reuptake and stimulating the release of dopamine and norepinephrine. This mechanism of action has been associated with the production of amphetamine-like effects and is supported by user reports of stimulant and mild psychoactive effects similar to those of amphetamine and MDMA. Further, as the drug's chemical structure allows it to be highly soluble and thus more easily cross the blood-brain barrier, a similar abuse liability profile to amphetamine may be expected. Taken together with the ease with which “bath salts” can be purchased, numerous routes of administration and unconfirmed user accounts of short duration of action, there may be preliminary indication that MDPV is likely to be abused. However, in the absence of clinical studies, by relying solely on sparse pharmacological data and indirect evidence suggestive of abuse liability, it is not possible to make a definitive statement of abuse liability.

At present, there is no focused research on the dependence potential of MDPV and other synthetic cathinones. While dopaminergic properties, particularly in the mesocorticolimbic system, might be considered a signal suggesting the presence of reinforcing properties, sound scientific evidence that MDPV possesses dependence potential is not available. Therefore, it is not possible to conclude whether MDPV does or does not have dependence potential.

References

1. Yohannan JC, Bozenko JS. The characterization of 3,4-methylenedioxypropylvalerone. *Microgram Journal*. 2010;7:12-5.
2. Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom*. 2010;24(18):2706-14.
3. Meyer MR, Du P, Schuster F, Maurer HH. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-propylvalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom*. 2010;45(12):1426-42.
4. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin Syndrome Associated With MDPV Use: A Case Report. *Ann Emerg Med*. 2011.
5. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila)*. 2011;49(6):499-505.
6. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit*. 2011;33(2):257-63.
7. Coppola M, Mondola R. 3,4-methylenedioxypropylvalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett*. 2012;208(1):12-5.
8. Drug & Chemical Evaluation Section. 3,4-Methylenedioxypropylvalerone (MDPV). US Drug Enforcement Administration, Control OoD; 2011.
9. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Propylvalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem*. 2006;49(4):1420-32.
10. Fuwa T., Fukumori N., Tanaka T., Kubo Y., Ogata A., Uehara S., et al. Microdialysis study of drug effects on central nervous system. Changes in dopamine levels in mice striatum after oral administration of methylenedioxypropylvalerone [in Japanese]. *Tokyo-to Kenko Anzen Kenkyu Senta Kenkyu Nenpo*. 2007;58:287-92.
11. Fuwa T., Kodama T., Honda Y., Tanaka T., Kubo Y., Ohashi N., et al. Influence of Methylenedioxypropylvalerone on Central Nervous System - Using Microdialysis Methods [in Japanese]. *ChemBio*. 2009;5:62-72.
12. Centre for Disease Control and Prevention (CDC). Emergency department visits after the use of a drug sold as "bath salts". Michigan: 2011.
13. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, et al. Energy-1 ('NRG-1'): don't believe what the newspapers say about it being legal. *Emerg Med J*. 2011;28(12):1068-70.

14. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: "Bath Salts". *Gen Hosp Psychiatry*. 2011;33(5):525-6.
15. Durham M. Ivory wave: the next mephedrone? *Emerg Med J*. 2011;28(12):1059-60.
16. Borek HA, Holstege CP. Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypropylone. *Ann Emerg Med*. 2012.
- ~~17. Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypropylone (MDPV). *J Med Toxicol*. 2012;8(1):69-75.~~
18. Kriikku P, Wilhelm L, Schwarz O, Rintatalo J. New designer drug of abuse: 3,4-Methylenedioxypropylone (MDPV). Findings from apprehended drivers in Finland. *Forensic Sci Int*. 2011;210(1-3):195-200.

124



For Your Review: Revised MDPV Notice & Workplan

Tara Phillips to: Jocelyn Kula

Cc: Nathan Isotalo

2012-04-30 05:07 PM

History: This message has been replied to.

Hi Jocelyn,

Please find attached revised versions of the MDPV Notice and Workplan. I have incorporated your comments of last Friday.

Thank you,

Tara



NOI MDPV 2012-04-30.doc



DRAFT MDPV WorkPlan Apr 30, 2012.doc

125

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

*Notice to interested parties – Proposed amendment to Schedule III to the Controlled
Drugs and Substances Act*

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's intent to add 3,4-methylenedioxypropylamphetamine (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule III to the *Controlled Drugs and Substances Act* (CDSA).

Health Canada is not aware of any legitimate medical, scientific or industrial applications for MDPV and is therefore not intending to regulate MDPV in accordance with existing regulatory schemes under the CDSA.

This proposed action is in response to recent increases in law enforcement and border seizures of products labelled as "bath salts". Such products are not genuine bath salt products intended for softening/cleansing the skin, but contain one or more substances with stimulant properties. MDPV poses a potential risk to the health and safety of Canadians because its use can result in increased blood pressure and increased heart rate, and has also been associated with panic attacks, anxiety, hallucinations, suicidal thoughts and death.

While the extent of their use in Canada is unknown, "bath salts" products are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky". "Bath salts" products have also been found to contain mephedrone and methylone, which are analogues of amphetamine and thus considered to be included in Schedule III to the CDSA.

Although MDPV is not listed in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have already elected to regulate it as a controlled substance including the United States, Australia, Denmark, Sweden and the United Kingdom.

Including MDPV in Schedule III to the CDSA would prohibit the following activities with this substance: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The scheduling of MDPV will also ensure law enforcement can take action against all suspected illegal activities involving MDPV.

The publication of this notice begins a 60-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D,

123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. In particular, parties involved in legitimate activities involving MDPV are encouraged to respond to inform Health Canada's decision with respect to regulation of MDPV under the CDSA.

CATHY SABISTON
Director General
Controlled Substance and Tobacco Directorate

WORKPLAN: Scheduling of MDPV under the *Controlled Drugs and Substances Act*

Task/Activity		Target Date	Lead	Status
TRIAGE STATEMENT				
1	Draft triage statement	May 4, 2012	RPD	Ongoing
2	Consult with Treasury Board Secretariat	May 11, 2012	RPD, TBS	Ongoing
3	Obtain Director approval of triage statement	May 18, 2012	RPD, DO	
4	Obtain TBS approval of triage statement	May 25, 2012	RPD, DGO	
NOTICE TO INTERESTED PARTIES (Notice) - for publication in <i>Canada Gazette, Part I</i>				
1	Draft Notice	April 27, 2012	RPD	Ongoing
2	Obtain Director approval of Notice	April 30, 2012	RPD, DO	
3	Obtain DG, CSTD approval of Notice	May 4, 2012	RPD, DGO	
4	Brief senior management (ADM/DM) on Notice, as required	May 11, 2012	RPD, DGO, ADMO	
5	Submission to Canada Gazette Directorate (6 working days in advance of publication date)	May 17, 2012	RPD, Canada Gazette Directorate	
6	Publication in <i>Canada Gazette, Part I</i>	May 26, 2012	Canada Gazette Directorate	
7	60-day comment period ends	July 25, 2012	RPD	
8	Review and analysis of comments received	August 3, 2012	RPD	

ISSUE ANALYSIS SUMMARY

1	Research & Analysis (including ORS contract on pharmacology)	May 25, 2012	RPD & ORS	Ongoing
2	Draft Issue Analysis Summary	June 8, 2012	RPD	Ongoing
3	Consultation with internal partners (DAS, ORS, etc.)	July	RPD	
4	Obtain Director, OCS approval of Issue Analysis Summary	July 27, 2012	RPD, DO	

REGULATORY PROPOSAL

Note: Provided that no legitimate industry is identified via *Notice to interested parties*, there will be no administrative burden or compliance burden associated with proposal. Therefore, Regulatory Cost Calculator results will not be required.

I. Preparation of Drafting Instructions

1	Prepare drafting instructions	June 8, 2012	RPD	
2	Legal Services Review of drafting instructions	June 29, 2012	LSU	
3	Translate drafting instructions	July 6, 2012	RPD	

II. Drafting and Review of Regulatory Text

5	Obtain Director, OCS approval of drafting instructions	August 2, 2012	RPD, DO	
6	Obtain DG, CSTD approval of drafting instructions	August 7, 2012	RPD, DGO	
7	Submit drafting instructions to Department of Justice Drafting Service	August 8, 2012	RPD	

s.21(1)(a)
s.21(1)(b)
000617

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Page(s) 000618 to\à 000618

**Is(Are) exempted pursuant to section(s)
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**

127



Re: For Action: Review of Draft MDPV Assessment 
Nathan Isotalo to: Tara Phillips

2012-05-01 09:11 AM

Good morning, Tara,

I am not sure why or who exactly proposed this contract.

As MDPV is not a drug, it has not undergone clinical trials nor would an abuse liability studies or an assessment have been performed.

I took a glance at the conclusions and sure enough, yes, no abuse liability studies or clinical trials were conducted... this is no surprise to me.

What matters is how users have experienced serious cravings upon use along with dependence. The data that exists comes from media reports and hospital reports and incidents mainly in the U.S..

Vlad Kushnir reports that "although one literature source cited the development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV these drug related effects could not be confirmed"

I can tell at a glance there was no attempt to summarize experiences of abuse / misuse/ dependence in North America.

This is where the human drug abuser data lies and I believe that it should be reported.

As for time, one day is really not adequate given

- 1) the serious nature of the file
- 2) the assessment is science based
- 3) competing priorities as the marihuana ATIP is now a priority aswell as the response has come back from ATIP office.

Nathan.

Tara Phillips

Hi Nathan, Please review the attached documen...

2012-04-30 04:59:06 PM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-04-30 04:59 PM
Subject: For Action: Review of Draft MDPV Assessment

Hi Nathan,

Please review the attached document and provide written comments to me by close of business tomorrow, Tuesday, May 1st. If this deadlines does not provide you with adequate time, please let me know at your earliest convenience and we can discuss.

Please use the checklist that I sent to you on April 17, 2012, to assess your written comments prior to submitting them to me.

Thank you,

000619

129

**3,4-Methylenedioxypropylone (MDPV) Abuse Liability and Dependence
Potential Assessment**

Prepared by Vlad Kushnir, MSc
April 30, 2012

3,4-Methylenedioxypropylvalerone (MDPV) Abuse Liability and Dependence Potential Assessment

Background

The synthetic cathinone 3,4-Methylenedioxypropylvalerone, also known as MDPV, is a designer drug that is used for its cocaine and amphetamine-like psychoactive effects. First synthesized and patented by Boehringer Ingelheim in 1969,¹ it has only recently gained exposure among recreational drug users. ~~It is one of a number synthetic cathinones that~~ are derivatives of the vegetable cathinone, a naturally occurring beta-ketone amphetamine analogue found in the leaves of *Catha edulis* (khat). Considered as "legal highs", synthetic cathinones are generally sold as "bath salts" or "plant food" and labelled "not for human consumption" to circumvent regulatory control and drug abuse legislation. MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities. The substance does not have any known medical uses and is an analogue of the compound propylvalerone (a Schedule ~~V~~ controlled substance).

→
to
keep
MDPV
described
as
derivative
of
propylvalerone

or
crystals
or
mills

IV

under the CDSA

Chemistry

Chemical Structure

The compound 3,4-Methylenedioxypropylvalerone (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5yl)-2-pyrrolidin-1-yl-pentan-1-one) is a pyrrolidine derivative of the synthetic cathinone propylvalerone, differing in the presence of a 3,4-methylenedioxy group linked to the aromatic ring.¹ Its molecular formula is C₁₆H₂₁NO₃ and has a molecular weight of 275.34284 g/mol; Chemical Abstract Service Number 687603-66-3. MDPV is a solid at room temperature and has a melting point of 209.3 °C and a boiling point of 476 °C. It is available as an amorphous solid or crystalline powder that varies in colour, depending on composition and added impurities. In the free base form it is brown or yellowish green, whereas as a hydrochloride salt it is white in appearance.

~~275.34284~~

Pharmacology

Biotransformation

The metabolism of MDPV has been evaluated only *in vitro* in two studies. Examination of MDPV metabolism in human liver cells has prompted the proposal of a metabolic pathway that involves first, the opening of the methylenedioxy ring, followed by demethylation that gives rise to a catechol ring, which is in turn methylated by catecholmethyltransferase.² The aromatic pyrrolidine ring and side chain are subsequently hydroxylated, followed by oxidation to the corresponding lactam, as well as ring opening to the corresponding carboxylic acid. It was documented that the demethylation step of the Phase I metabolism, in particular, is catalyzed

yes
demethylation
of
PK I, II
metabolism

through CYP450 isozymes 2C19, 2D6 and 1A2.³ Approximately 80% of MDPV remains unmetabolized, 10% is metabolized into cetechol pyrovalerone, and 7% is metabolized into methylcatechol pyrovalerone. The high percentage of the parent compound was postulated to remain as a result of very high concentrations of MDPV added to liver microsome samples. Nevertheless, it was determined that the main metabolites further undergo Phase II glucoronidation and sulfation transformations to allow for renal excretion.²

not metabolized

Elimination

The excretion profile of MDPV and its metabolites has not been studied in animals or humans. However, several reports have documented MDPV concentrations in urine samples obtained from patients presenting to hospital and poison centres, as well as opioid dependent patients undergoing opioid substitution treatment. MDPV concentrations in urine have been noted to range from 0.034 – 3.9 mg/L in those cases.⁴⁻⁶ While anecdotal reports indicate that users ingest anywhere between 5 – 30mg of MDPV per single session,⁶⁻⁸ variable dose intake among users and undocumented time since ingestion prohibit from determining the MDPV elimination half-life and concentration of excreted metabolites.

Pharmacological Mechanism of Action

The exact mechanism of action of MDPV has not been fully elucidated, with only a handful of studies investigating its neurobiological effects. *In-vitro*, MDPV has demonstrated to act as a potent dopamine ($IC_{50} = 52.0 \pm 20$ nM) and norepinephrine ($IC_{50} = 28.3 \pm 8.1$ nM) reuptake inhibitor, exhibiting dopamine and norepinephrine reuptake inhibition 9 and 13 times greater than cocaine, respectively. In contrast, inhibition of serotonin reuptake was found to be markedly less pronounced ($IC_{50} = 2780 \pm 590$ nM), a finding that reflected in the reduced binding affinity for the serotonergic transporter.⁹ Microdialysis studies in freely moving mice supported the *in-vitro* findings, showing that 60 minutes following oral administration of MDPV, extracellular striatum dopamine content was 2.1 times higher in the experimental group compared to those in the control group. While substantial, MDPV induced increases in dopamine levels, however, were milder than those produced by the amphetamine-like stimulants methamphetamine and methylenedioxymethamphetamine (MDMA). Further, serotonin concentrations were not significantly influenced by MDPV administration.^{10, 11}

→ this points need to be highlighted expanded on due to drug potential as per

Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. MDPV binding affinities at the dopamine transporter ($K_i = 21.4 \pm 4.6$ nM) and norepinephrine transporter ($K_i = 195 \pm 26$ nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively. Binding affinity for the serotonin transporter was considerably lower ($K_i = 3770 \pm 560$ nM), indicating that MDPV is relatively inactive at this site.⁹

→ binding affinity to dopamine transporter

Human Toxicology

At present, a toxicological profile for MDPV, including a dose-response relationship and the median lethal dose (LD₅₀), has not yet been established. Primary indication of MDPV toxicity in the scientific community has developed from case reports documenting individuals presenting to hospital emergency departments after intake of "bath salts". The most common symptoms of acute toxicity involve those associated with cardiovascular, neurological, and psychopathological function. Specifically, they include: tachycardia, chest pain, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, delusions, auditory and visual hallucinations, paranoid psychosis, agitation, aggression, anxiety, panic attacks, insomnia, memory loss, hyperthermia, rhabdomyolysis, abdominal pain, decreased appetite, vomiting, and kidney dysfunction.^{4, 12-17} Some effects such as sleeping difficulties, anxiety and agitation have been reported to persist for more than one day following ingestion,¹³ while others have been suggested to continue for as long as a week.¹⁵ Several cases of drug-induced delirium and even death have also been noted, where MDPV was the sole intoxicant.¹⁴

¹⁷ Most commonly, however, as MDPV is co-ingested with other substances, including benzodiazepines, amphetamines, cannabis, and ethanol,^{5, 18} it is unclear whether the list of acute toxic effects is purely a result of MDPV or a combination of drug-drug interactions.

Not documented as reported in medicine... related to MDPV in most severe cases.

Case studies should be presented in table of findings

Evidence of Abuse Liability

Animal or human laboratory studies on abuse liability of MDPV have not been carried out. Specifically, the most common approaches used to investigate abuse potential of drugs in animals, namely, self-administration tests, conditioned place preference, drug discrimination, and psychomotor tests are not documented in the scientific literature. Similarly, abuse liability trials in recreational drug users using double blind, randomized, double dummy, placebo or positive comparator controlled, or crossover designs have not been conducted. Only one study has made an inference to MDPV being liable to abuse. Through the use of the gas chromatography-mass spectrometry procedure to detect MDPV and other substances in urine of opioid-dependent patients undergoing opioid substitution treatment, the authors suggested that MDPV is mainly used a "non-detectable" substitute for amphetamine primarily to increase concentration among users. Moreover, they emphasized that the inability to detect MDPV through conventional immunoassay drug screenings is a notable factor that may contribute to the drug's misuse.⁶

The numerous case reports of acute MDPV intoxication highlighted in the scientific literature may be in their own respect, an indirect indication that the drug may possess abuse potential. Among recreational drug users, MDPV ^{has gained} may be gaining popularity specifically for its anecdotal desired subjective effects. Synthesizing internet information on the effects of MDPV, one review has noted that specifically at low doses (undefined), MDPV is used to increase concentration, the capacity to work, and sexual performance. Other desired psychotomimetic effects include increased sociability, energy, limited euphoria, and mild empathogenic effects.⁷

abuse and has reached epidemic levels in the U.S.

Evidence of Physical Dependence

Behavioural animal data on the reinforcing and physical dependence-producing effects of MDPV is not available. Clinical trials on MDPV abuse liability have also not been conducted, therefore scientific evidence of tolerance or withdrawal, which is critical to the definition of physical dependence, has not been observed. Although one literature source cited the "development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV",⁷ these drug-related effects could not be confirmed.

Evidence of possible physical dependence and tolerance building effects is indirect and can only be gleaned from case studies and unverified internet information reported by users. Penders and Gestring¹⁴ reported of a woman admitted to the psychiatric unit of a community hospital by way of an involuntary commitment initiated by her husband. The individual experienced fearful hallucinations of a home invasion that precipitated following daily use of MDPV for 2 weeks prior to admission. It is possible to infer that repeated and perhaps uncontrollable use of the drug is suggestive of physical dependence-like effects, however, this conclusion is highly speculative. Indication of possible tolerance is based on internet discussions documenting common redosing in a single session as well as using doses of over 200mg.⁷ Although MDPV is reported to have a short duration of action, use of doses well over 6 times the typical 5 to 30 mg used in a single ingestion, suggests that users may develop tolerance to the drug's effects and thus possible physical dependence.

no mention of tolerance?

There have been several instances of experimental dose demonstrating significant strong cravings resulting in continuation of administration, leading to self mutilation and suicide.

Conclusions

The abuse potential assessment of a drug should be based on a composite analysis of chemistry, pharmacology, clinical data, health risks that the drug presents, as well as ease of access to the drug and administration. The limited pharmacological data suggests that MDPV is similar to other synthetic cathinones, inhibiting reuptake and stimulating the release of dopamine and norepinephrine. This mechanism of action has been associated with the production of amphetamine-like effects and is supported by user reports of stimulant and mild psychoactive effects similar to those of amphetamine and MDMA. Further, as the drug's chemical structure allows it to be highly soluble and thus more easily cross the blood-brain barrier, a similar abuse liability profile to amphetamine may be expected. Taken together with the ease with which "bath salts" can be purchased, numerous routes of administration and unconfirmed user accounts of short duration of action, there may be preliminary indication that MDPV is likely to be abused. However, in the absence of clinical studies, by relying solely on sparse pharmacological data and indirect evidence suggestive of abuse liability, it is not possible to make a definitive statement of abuse liability.

This demonstrates sign. phys. dependence and needs to be presented.

At present, there is no focused research on the dependence potential of MDPV and other synthetic cathinones. While dopaminergic properties, particularly in the mesocorticolimbic system, might be considered a signal suggesting the presence of reinforcing properties, sound scientific evidence that MDPV possesses dependence potential is not available. Therefore, it is not possible to conclude whether MDPV does or does not have dependence potential.

Please provide an overview of all MDPV media reports for North America since

References

1. Yohannan JC, Bozenko JS. The characterization of 3,4-methylenedioxypropylvalerone. *Microgram Journal*. 2010;7:12-5.
2. Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylvalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom*. 2010;24(18):2706-14.
3. Meyer MR, Du P, Schuster F, Maurer HH. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-propylvalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom*. 2010;45(12):1426-42.
4. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin Syndrome Associated With MDPV Use: A Case Report. *Ann Emerg Med*. 2011.
5. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila)*. 2011;49(6):499-505.
6. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit*. 2011;33(2):257-63.
7. Coppola M, Mondola R. 3,4-methylenedioxypropylvalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett*. 2012;208(1):12-5.
8. Drug & Chemical Evaluation Section. 3,4-Methylenedioxypropylvalerone (MDPV). US Drug Enforcement Administration, Control OoD; 2011.
9. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem*. 2006;49(4):1420-32.
10. Fuwa T., Fukumori N., Tanaka T., Kubo Y., Ogata A., Uehara S., et al. Microdialysis study of drug effects on central nervous system. Changes in dopamine levels in mice striatum after oral administration of methylenedioxypropylvalerone [in Japanese]. *Tokyo-to Kenko Anzen Kenkyu Senta Kenkyu Nenpo*. 2007;58:287-92.
11. Fuwa T., Kodama T., Honda Y., Tanaka T., Kubo Y., Ohashi N., et al. Influence of Methylenedioxypropylvalerone on Central Nervous System - Using Microdialysis Methods [in Japanese]. *ChemBio*. 2009;5:62-72.
12. Centre for Disease Control and Prevention (CDC). Emergency department visits after the use of a drug sold as "bath salts". Michigan: 2011.
13. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, et al. Energy-1 ('NRG-1'): don't believe what the newspapers say about it being legal. *Emerg Med J*. 2011;28(12):1068-70.

14. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: "Bath Salts". *Gen Hosp Psychiatry*. 2011;33(5):525-6.
15. Durham M. Ivory wave: the next mephedrone? *Emerg Med J*. 2011;28(12):1059-60.
16. Borek HA, Holstege CP. Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypropylone. *Ann Emerg Med*. 2012.

17. Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypropylone (MDPV). *J Med Toxicol*. 2012;8(1):69-75.
18. Kriikku P, Wilhelm L, Schwarz O, Rintatalo J. New designer drug of abuse: 3,4-Methylenedioxypropylone (MDPV). Findings from apprehended drivers in Finland. *Forensic Sci Int*. 2011;210(1-3):195-200.



Re: as discussed 
Nathan Isotalo to: Tara Phillips

2012-05-01 11:19 AM

Hi Tara,

as mentioned a few points for consideration; despite indirect evidence, this anecdotal evidence and hospital report data is largely undisputed and the media reports the past five years and incidence reporting in the U.S. forms a large part of the current knowledge of this drug of abuse.

In terms of past incidents where abusers develop such intense cravings as to seek out MDPV and continue to abuse leading in some cases to self mutilation and death should be enough to flag that hey...there is indeed a serious problem here with abuse, physical dependence so despite no actual formal clinical/abuse liability /physical dependence empirical evidence, there is some indirect and anecdotal physical dependence and abuse evidence associated with MDPV.

It is reported that "most commonly..." abuse of MDPV is with other substances of abuse. It would be better if the "most commonly" was removed as this may or may not be the case here in Canada or in North America. It would be better if it was written as "Incidents of abuse of MDPV/bath salts may or may not occur with the abuse of other substances such as alcohol, or other drugs of abuse." For the "tolerance" comment, you can treat as "stat" as I sped read over that part and notice he included internet data which is fine.

Overall, it seems representative of what I have seen in other published attempts to identify the current "scientific empirical evidence" understanding of MDPV/bathsalts. There is however, a need to highlight certain aspects...e.g. linkage of binding to dopamine receptors and 9-13X reuptake inhibition than cocaine with abuse potential.

Nathan.

Nathan Isotalo Hi Tara, please find attached my comments for t...

2012-05-01 10:02:31 AM

From: Nathan Isotalo/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-01 10:02 AM
Subject: Fw: Attached Image

Hi Tara,

please find attached my comments for the contractor's report-
Nathan.

----- Forwarded by Nathan Isotalo/HC-SC/GC/CA on 2012-05-01 10:01 AM -----

From: 0905-311A-CANNON6075MFP@hc-sc.gc.ca
To: "NATHAN ISOTALO" <nathan.isotalo@hc-sc.gc.ca>, "tara phillips" <tara.phillips@hc-sc.gc.ca>
Date: 2012-05-01 10:01 AM
Subject: Attached Image

[attachment "0388_001.pdf" deleted by Nathan Isotalo/HC-SC/GC/CA]

131



OCS Comments on Draft MDPV assessment for consideration

Tara Phillips to: Erin Rutherford

2012-05-02 02:06 PM

Cc: Jocelyn Kula, Nathan Isotalo

Hi Erin,

Thanks for the opportunity to comment on the draft MDPV assessment. Our comments are as follows:

- In paragraph 1, the final sentence should say that pyrovalerone is on Schedule IV to the CDSA (it says Schedule V right now and does not specifically reference the CDSA).
- Also in paragraph 1, could we say that MDPV is sold as a powder, crystal and pills since there have been reports of all three?
- For the Background and Chemical Structure sections, we need to consider the outstanding question of how we characterize MDPV. For example, in the Background paragraph, the statement that MDPV is one of a number of synthetic cathinones that are derivatives of the vegetable cathinone could be rejected if the decision is made to describe MDPV as a derivative of pyrovalerone.
- It would be very useful to strengthen the assessment in terms of abuse potential in two ways:
 - 1) by highlighting or emphasizing the point about receptor binding affinities being many times that of cocaine for particular receptors and explicitly linking those affinities to abuse potential
 - 2) by including references to anecdotal evidence of abuse, e.g., intensity of cravings, continued abuse despite significant adverse effects to users, etc.
- It would be helpful to include information about tolerance, if available.

Thank you,

Tara

----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2012-04-30 01:48 PM -----

From: Erin Rutherford/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-04-30 01:43 PM
Subject: Draft MDPV assessment for comments

Attached please find a draft MDPV assessment for your review and comments.



MDPV Assessment DRAFT.doc

I would appreciate if you could provide me with any comments prior to COB Wednesday.

Regards

Erin Rutherford

Manager/Gestionnaire
Drugs and Alcohol Research/Recherche, drogues et alcool
Office of Research and Surveillance / Bureau de la recherche et de la surveillance
Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au tabagisme

000628

132



Re:MDPV 
Nathan Isotalo to: Tara Phillips

2012-05-04 07:24 AM

Hi Tara,

fyi- something I wished to share with you yesterday.

I came across a reference yesterday on penalties of the CDSA Schedules and how they are to be interpreted.

In this regard, there are no penalties for possession for Sch IV substances. It appears that we need at the minimum Schedule III penalties for possession for MDPV...maybe even those of Schedule I.

I noticed in the NOI you indicated to add MPDV to Schedule III. I am o.k. with this however, if we consider as an analogue of amphetamines...then it will become a Schedule I from the new Safe Streets and Communities Act which has stricter penalties and a better deterrent for illicit activities. For consideration, we may also wish to move pyrovalerone to Sch III at the same time we add MDPV.

In my opinion, I believe that if the CDSA were ever to be amended, that penalties for possession should be included for Sch IV substances.

Thank you.

Nathan.

Tara Phillips | Hi Jocelyn, Please find attached revised version... | 2012-04-30 05:07:12 PM

From: Tara Phillips/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Cc: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-04-30 05:07 PM
Subject: For Your Review: Revised MDPV Notice & Workplan

Hi Jocelyn,

Please find attached revised versions of the MDPV Notice and Workplan. I have incorporated your comments of last Friday.

Thank you,

Tara

[attachment "NOI MDPV 2012-04-30.doc" deleted by Nathan Isotalo/HC-SC/GC/CA] [attachment "DRAFT MDPV WorkPlan Apr 30, 2012.doc" deleted by Nathan Isotalo/HC-SC/GC/CA]

133



Fw: MDPV assessment - comments from OCS
Nathan Isotalo to: Tara Phillips

2012-05-04 07:40 AM

Hi Tara

fyi- In regards to this proposed response, this is the part of the report that applies (in bold); also for the norepinephrine transporter, it would be more useful to know how MDPV competes with norepinephrine (NE) for the norepinephrine transporter and not just how it compares to cocaine.

"Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. **MDPV binding affinities at the dopamine transporter ($K_i = 21.4 \pm 4.6$ nM) and norepinephrine transporter ($K_i = 195 \pm 26$ nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively."**

----- Forwarded by Nathan Isotalo/HC-SC/GC/CA on 2012-05-04 07:32 AM -----

From: Nathan Isotalo/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-03 03:01 PM
Subject: Re: MDPV assessment - comments from OCS

Hi Tara

In regards to our first comment, the binding of MDPV to the dopamine transporter is much more greater than cocaine. This is very important as cocaine acts to block the DAT active- ransporter.

This affects how dopamine is re-uptaken from the synapse resulting in more dopamine being available to bind to receptors and cause euphoria causing increased potential for abuse.

Nathan.

Erin Rutherford Thanks so much for taking the time to review th... 2012-05-03 01:39:11 PM

From: Erin Rutherford/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Cc: Jocelyn Kula/HC-SC/GC/CA@HWC, Nathan Isotalo/HC-SC/GC/CA@HWC, Suzanne Desjardins/HC-SC/GC/CA@HWC
Date: 2012-05-03 01:39 PM
Subject: MDPV assessment - comments from OCS

Thanks so much for taking the time to review the paper.

We've considered all your comments and have responded in red below, for your information.

We will be sending the comments to the contractor later today and will have the final report in one week.

Please don't hesitate to contact me if you have any comments, question or concerns.

Thanks

Erin

000630

- In paragraph 1, the final sentence should say that pyrovalerone is on Schedule IV to the CDSA (it says Schedule V right now and does not specifically reference the CDSA). Agreed

- Also in paragraph 1, could we say that MDPV is sold as a powder, crystal and pills since there have been reports of all three? If confirmed by DAS? ORS will check

~~- For the Background and Chemical Structure sections, we need to consider the outstanding question of how we characterize MDPV. For example, in the Background paragraph, the statement that MDPV is one of a number of synthetic cathinones that are derivatives of the vegetable cathinone could be rejected if the decision is made to describe MDPV as a derivative of pyrovalerone. Not appropriate for this document but certainly needs to be considered by OCS~~

- It would be very useful to strengthen the assessment in terms of abuse potential in two ways:

1) by highlighting or emphasizing the point about receptor binding affinities being many times that of cocaine for particular receptors and explicitly linking those affinities to abuse potential Receptor binding affinity does not say anything about a substance's abuse potential. Making such a prediction or assessment requires many different types of data (which include receptor binding studies, but also include *in vitro* efficacy/potency studies, *in vivo* behavioural studies and human data).

2) by including references to anecdotal evidence of abuse, e.g., intensity of cravings, continued abuse despite significant adverse effects to users, etc. Anecdotal evidence is not appropriate for this document but could be included by OCS in IAS

- It would be helpful to include information about tolerance, if available. Agreed (if data available)

134



Re:MDPV
Nathan Isotalo to: Tara Phillips

2012-05-04 09:45 AM

Hi Tara,

To clarify, at the time of drafting the triage/ IAS, Schedule IV was recommended because pyrovalerone is on schedule IV and it is a derivative of pyrovalerone and in the past RPD had placed substances on schedules based on substance groupings.

In this case, given the harm associated with MDPV, I had suggested possibly seeking a legal opinion on appropriate penalties we might consider that might impact where it should be scheduled.

I am not aware if any opinion was ever sought or not.

Under possession, Schedule IV covers off double doctoring as an indictable offence of 18 months but you are correct, there are no penalties for anyone caught for simple possession e.g. with MDPV at raves. Possession under 4(1) of CDSA applies to Schedules I, II, and III.

You can note that I am fine with placing MDPV on Schedule III and that if we ever were to engage in amending the CDSA, we might consider discussing with legal as to the benefits of applying possession penalties to other Schedules other than I, II and III.

Nathan.

Tara Phillips

Hi Nathan, As you will recall, when we discusse...

2012-05-04 09:05:36 AM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-05-04 09:05 AM
Subject: Re:MDPV

Hi Nathan,

As you will recall, when we discussed your recommendation for Schedule IV for MDPV last week, I pointed out that Schedule IV doesn't prohibit simple possession and that was one of the reasons why I felt Schedule III would perhaps be more appropriate. We also discussed the possibility of Schedule I and the CCSA. Given this discussion, I am not clear as to the purpose of your email below. Am I understanding correctly that it is simply to note your view that penalties for possession should be included for Sch IV substances?

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

Nathan Isotalo

Hi Tara, fyi- something I wished to share with yo...

2012-05-04 07:24:27 AM

From: Nathan Isotalo/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-04 07:24 AM
Subject: Re:MDPV

Hi Tara,

~~fyi- something I wished to share with you yesterday.~~

I came across a reference yesterday on penalties of the CDSA Schedules and how they are to be interpreted.

In this regard, there are no penalties for possession for Sch IV substances. It appears that we need at the minimum Schedule III penalties for possession for MDPV...maybe even those of Schedule I.

I noticed in the NOI you indicated to add MPDV to Schedule III. I am o.k. with this however, if we consider as an analogue of amphetamines...then it will become a Schedule I from the new Safe Streets and Communities Act which has stricter penalties and a better deterrent for illicit activities. For consideration, we may also wish to move pyrovalerone to Sch III at the same time we add MDPV.

In my opinion, I believe that if the CDSA were ever to be amended, that penalties for possession should be included for Sch IV substances.

Thank you.

Nathan.

Tara Phillips

Hi Jocelyn, Please find attached revised version...

2012-04-30 05:07:12 PM

135



Fw: re methylone
Nathan Isotalo to: Tara Phillips

2012-05-04 02:54 PM

----- Forwarded by Nathan Isotalo/HC-SC/GC/CA on 2012-05-04 02:54 PM -----

From: Evelyn Soo/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Cc: Status/HC-SC/GC/CA@HWC
Date: 2012-03-09 11:56 AM
Subject: Re: re methylone

Hi Nathan

Yes, status is CONTROLLED under item 1 of Schedule III to the CDSA.

Evelyn

Evelyn C Soo, PhD
A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé
environnementale et de la sécurité des consommateurs (DGSESC)
Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
evelyn.soo@hc-sc.gc.ca
Telephone | Téléphone 613-954-1758
Government of Canada | Gouvernement du Canada

Nathan Isotalo Good morning, Evelyn do you have a status dec... 2012-03-09 11:22:02 AM

From: Nathan Isotalo/HC-SC/GC/CA
To: Evelyn Soo/HC-SC/GC/CA@HWC
Date: 2012-03-09 11:22 AM
Subject: re methylone

Good morning, Evelyn

do you have a status decision on "methylone"? I suspect that it would be an Sch. III analogue of
cathinone. Chem name: 3,4-methylenedioxy-N-methylcathinone.

thank you. Nathan.

136



Fw: Information inquiry re: 'Bath Salts'
Jocelyn Kula to: Nathan Isotalo
Cc: Tara Phillips

2012-05-10 01:45 PM

for our corporate file pls

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224
---- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2012-05-10 01:45 PM ----

From: Suzanna Keller/HC-SC/GC/CA
To: Evelyn Soo/HC-SC/GC/CA@HWC
Cc: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-05-10 12:32 PM
Subject: Re: Information inquiry re: 'Bath Salts'

Thank you, Evelyn, for these added details.

Much appreciated.
Suzanna

Evelyn Soo Hi Jocelyn I spoke to Suzanna about this and sh... 2012-05-10 12:28:17 PM

From: Evelyn Soo/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Cc: Suzanna Keller/HC-SC/GC/CA@HWC
Date: 2012-05-10 12:28 PM
Subject: Re: Information inquiry re: 'Bath Salts'

Hi Jocelyn

I spoke to Suzanna about this and she is aware that questions on scheduling should be directed to your shop as we only do status decisions.

As for mephedrone, the substance was included under the item 1 of Schedule III to the CDSA on the basis that it is an amphetamine analogue. Specifically, it is considered an analogue of 4-methylmethamphetamine.

Hope this helps.

Best wishes
Evelyn

Evelyn C Soo, PhD
A/Manager, Research on Tobacco | Gestionnaire intérimaire, Recherche sur le tabac
Office of Research and Surveillance | Bureau de la recherche et de la surveillance
Healthy Environments and Consumer Safety Branch (HECSB) | Direction générale de la santé environnementale et de la sécurité des consommateurs (DGSESC)

Health Canada | Santé Canada
123 Slater St. Ottawa ON K1A 0K9 | 123 rue Slater Ottawa ON K1A 0K9
evelyn.soo@hc-sc.gc.ca
Telephone | Téléphone 613-952-2514
Government of Canada | Gouvernement du Canada

Suzanna Keller Thank you, Jocelyn. This is very helpful.

2012-05-10 12:21:38 PM



Re: Fw: MDPV Abuse Liability and Dependence Assessment 
Nathan Isotalo to: Tara Phillips

2012-05-18 11:06 AM

Thank you. Tara.

Yes, as required, we will update any documents as needed based on any new templates of Treasury Board.

I believe that Vladimir is right when he says that no scientific or randomized control studies have been conducted.

Importantly, this does not preclude any dependence issues associated with MDPV. Human experience data as reported from media coverage and hospital data provides indirect evidence of MPDV abuse with a potential to cause psychological and/or physical dependence. This evidence suggests that there is a likelihood of psychological/physical dependence issues with MDPV which requires further investigation. For these cases, users appear to be compelled to take more or higher doses that are more likely to cause more serious adverse health effects.

In the absence on conclusive results, we can recommend scheduling based on application of the precautionary principle.

Nathan.

Tara Phillips

Hi Nathan, See below.

2012-05-18 10:30:39 AM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-05-18 10:30 AM
Subject: Fw: MDPV Abuse Liability and Dependence Assessment

Hi Nathan,

See below.

I have a request in to Kyle Burns because I have heard that TBS released a new template for the Triage Statement, which reflects the reforms being implemented. I will let you know when I hear back so that we can move forward with that document.

Thank you,

Tara

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-18 10:29 AM -----

From: Erin Rutherford/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC, Tara Phillips/HC-SC/GC/CA@HWC
Cc: Suzanne Desjardins/HC-SC/GC/CA@HWC, Hanan Abramovici/HC-SC/GC/CA@HWC
Date: 2012-05-16 01:55 PM
Subject: MDPV Abuse Liability and Dependence Assessment

Attached please find the final MDPV Abuse Liability and Dependence Assessment prepared for Health Canada by Vlad Kushnir.

Regards

Erin Rutherford

Manager/Gestionnaire

Drugs and Alcohol Research/Recherche, drogues et alcool

Office of Research and Surveillance / Bureau de la recherche et de la surveillance

Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au
tabagisme

Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et
de la sécurité des consommateurs

Health Canada / Santé Canada

123 Slater, MacDonald Building

Room A616 Address Locator: AL 3506 D

Ottawa, Ontario K1A 0K9

Telephone: (613) 954-2210

Fax: (613) 952-5188

E-mail: erin.rutherford@hc-sc.gc.ca

[attachment "MDPV Assessment Final.doc" deleted by Nathan Isotalo/HC-SC/GC/CA]

139

**3,4-Methylenedioxypropylone (MDPV) Abuse Liability and Dependence
Potential Assessment**

Prepared by: Vlad Kushnir, MSc
May 11, 2012

3,4-Methylenedioxypropylamphetamine (MDPV) Abuse Liability and Dependence Potential Assessment

Background

The synthetic cathinone 3,4-Methylenedioxypropylamphetamine, also known as MDPV, is a designer drug that is used for its stimulant-like psychoactive effects.^{1, 2} First synthesized and patented by Boehringer Ingelheim in 1969,³ it has only recently gained exposure among recreational drug users. It is one of a number synthetic cathinones that are derivatives of cathinone, a naturally occurring beta-ketone amphetamine analogue found in the leaves of *Catha edulis* (khat).⁴ Synthetic cathinones are generally sold as “bath salts” or “plant food” and labelled “not for human consumption” to circumvent regulatory control and drug abuse legislation. As such, they are considered “legal highs”. MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities, with oral ingestion, injection, and nasal insufflation being most prevalent.^{2, 5} The substance does not have any known medical uses and is an analogue of the compound propylamphetamine (a Schedule V controlled substance under the Controlled Drugs and Substances Act).

Chemistry

Chemical Structure

The compound 3,4-Methylenedioxypropylamphetamine (MDPV) (IUPAC name: 1-(1,3-benzodioxol-5yl)-2-pyrrolidin-1-yl-pentan-1-one) is a pyrrolidine derivative of the synthetic cathinone propylamphetamine, differing in the presence of a 3,4-methylenedioxy group linked to the aromatic ring.³ Its molecular formula is C₁₆H₂₁NO₃ and it has a molecular weight of 275.34284 g/mol; Chemical Abstract Service Number 687603-66-3. MDPV is a solid at room temperature and has a melting point of 238-239 °C.³ It is available as an amorphous solid or crystalline powder that varies in colour, depending on composition and added impurities.⁶ In the free base form it is brown or yellowish green, whereas as a hydrochloride salt it is white in appearance.¹

Pharmacology

Biotransformation

Very little information is available regarding the metabolism of MDPV and what little is known comes from only two *in vitro* studies.^{7, 8} Examination of MDPV metabolism in human liver microsomes has prompted the proposal of a metabolic pathway that involves first, the opening of the methylenedioxy ring, followed by demethylation that gives rise to a catechol ring, which is in turn methylated by catecholmethyltransferase.⁸ The aromatic pyrrolidine ring and side chain are subsequently hydroxylated, followed by oxidation to the corresponding lactam, as well as ring opening to the corresponding carboxylic acid. It was documented that the

demethylation step of the Phase I metabolism, in particular, is catalyzed through CYP450 isozymes 2C19, 2D6 and 1A2.⁷ Approximately 80% of MDPV remains unmetabolized, 10% is metabolized into catechol pyrovalerone, and 7% is metabolized into methylcatechol pyrovalerone. The high percentage of unmetabolized parent compound was postulated to result from the very high concentrations of MDPV added to liver microsome samples. Nevertheless, it was determined that the main metabolites further undergo Phase II glucuronidation and sulfation transformations to allow for renal excretion.⁸

Elimination

The excretion profile of MDPV and its metabolites has not been studied in animals or humans. However, several reports have documented MDPV concentrations in urine samples obtained from patients presenting to hospital and poison centres, as well as opioid dependent patients undergoing opioid substitution treatment. MDPV concentrations in urine have been noted to range from 0.034 – 3.9 mg/L in those cases.^{6, 9, 10} While anecdotal reports indicate that users ingest anywhere between 5 – 30mg of MDPV per single session,^{1, 10, 11} variable dose intake among users and undocumented time since ingestion prohibit from determining the MDPV elimination half-life and concentration of excreted metabolites.

Pharmacological Mechanism of Action

The exact mechanism of action of MDPV has not been fully elucidated, with only a handful of studies investigating its neurobiological effects.¹²⁻¹⁴ Binding assays evaluating inhibition of monoamine uptake in competition with [³H]dopamine, [³H]serotonin, and [³H]norepinephrine revealed that MDPV is a potent dopamine (IC₅₀ = 52.0 ± 20 nM) and norepinephrine (IC₅₀ = 28.3 ± 8.1 nM) reuptake inhibitor, exhibiting reuptake inhibition 9 and 13 times greater than cocaine, respectively.¹⁴ In contrast, inhibition of serotonin reuptake was found to be markedly less pronounced (IC₅₀ = 2780 ± 590 nM), a finding supported by the observed reduced binding affinity for the serotonergic transporter.¹⁴ Microdialysis studies in freely moving mice supported some of the *in-vitro* findings, showing that 60 minutes following oral administration of MDPV, extracellular striatum dopamine content was 2.1 times higher in the experimental group compared to those in the control group.¹² While significant, the MDPV-induced increases in dopamine levels were 3.5 times lower than those found to be produced by the amphetamine-like stimulants methamphetamine and methylenedioxyamphetamine (MDMA) in the rat caudate.¹⁵ Further, serotonin concentrations were not significantly influenced by MDPV administration.^{12, 13}

Receptor Binding Affinities

MDPV receptor binding affinity has only been examined at the dopamine, norepinephrine, and serotonergic transporters. MDPV binding affinities at the dopamine transporter (K_i = 21.4 ± 4.6 nM) and norepinephrine transporter (K_i = 195 ± 26 nM) were shown to be 20 and 11 times more potent than that of cocaine, respectively.¹⁴ Binding affinity for the serotonin transporter was considerably lower (K_i = 3770 ± 560 nM), indicating that MDPV is relatively inactive at this site.¹⁴

Human Toxicology

At present, a toxicological profile for MDPV, including a dose-response relationship and the median lethal dose (LD₅₀), has not yet been established. Primary indication of MDPV toxicity is derived from case reports documenting individuals presenting to hospital emergency departments after intake of "bath salts". The most common symptoms of acute toxicity involve those associated with cardiovascular, neurological, and psychopathological function. Specifically, these symptoms include: tachycardia, chest pain, hypertension, hyperthermia, mydriasis, dizziness, tremors, psychomotor agitation, motor automatisms, delusions, auditory and visual hallucinations, paranoid psychosis, agitation, aggression, anxiety, panic attacks, insomnia, memory loss, hyperthermia, rhabdomyolysis, abdominal pain, decreased appetite, vomiting, and kidney dysfunction.^{5, 9, 16-20} Some effects such as sleeping difficulties, anxiety and agitation have been reported to persist for more than one day following ingestion,¹⁶ while others have been suggested to continue for as long as a week.¹⁸ Several cases of drug-induced delirium and even death have also been noted, where MDPV was the sole intoxicant.^{17, 20} However, as MDPV is most commonly co-ingested with other substances, including benzodiazepines, opiates, amphetamines, cannabis, and ethanol,^{1, 5, 6, 21} it is unclear whether the list of acute toxic effects is purely a result of MDPV or drug-drug interactions.

Routes of Administration

Information obtained from case reports and internet discussions about MDPV reveal that the drug is administered via a number of modalities. Routes of MDPV administration include intravenous, intramuscular, sublingual, oral ingestion, smoking, nasal insufflation, inhalation, as well as rectal administration.^{1, 5, 10, 20} Extrapolating from case reports of acute MDPV intoxication, it appears that the drug is most commonly administered by way of oral ingestion, nasal insufflation, or injection.^{16-18, 20}

Evidence of Abuse Liability

Animal or human laboratory studies on abuse liability of MDPV have not been carried out. The most common approaches used to investigate abuse potential of drugs in animals, namely, self-administration tests, conditioned place-preference, drug discrimination, and psychomotor tests are not documented in the scientific literature. Similarly, abuse liability studies in recreational drug users using double-blind, randomized, double-dummy, placebo or positive comparator controlled, or crossover designs have not been conducted. Only one study has made an inference to MDPV being liable to abuse.¹⁰ Through the use of the gas chromatography-mass spectrometry procedure to detect MDPV and other substances in urine of opioid-dependent patients undergoing opioid substitution treatment, the authors suggested that MDPV is mainly used as a "non-detectable" substitute for amphetamine. The inability to detect MDPV through conventional immunoassay drug screenings is indeed a notable factor that may contribute to the drug's likelihood for abuse, especially among those wishing to conceal illicit drug use.¹⁰

The numerous case reports of acute MDPV intoxication highlighted in the scientific literature may be in their own respect, an indirect indication that the drug may possess abuse

potential. Among recreational drug users, it appears that MDPV may be gaining popularity specifically for its anecdotally-described desirable subjective psychotropic effects. Synthesizing internet information on the effects of MDPV, one literature review has noted that specifically at low doses (undefined), MDPV is used to increase concentration, the capacity to work, and sexual performance.¹ Other desired psychotomimetic effects include increased sociability, energy, limited euphoria, and mild empathogenic effects.¹ Based on information available on the internet, the European Union Commission funded Psychonaut Web Mapping Project, documented that MDPV has a relatively short duration of action, with peak effects occurring at 90 min post ingestion and lasting for approximately 1 hour.²² The various desirable effects and their duration vary greatly however, depending on dose and individual.

Evidence of Physical Dependence

Behavioural animal data on the reinforcing and physical dependence-producing effects of MDPV is not available. Clinical trials on MDPV abuse liability have also not been conducted, therefore tolerance or withdrawal, which is critical to the definition of physical dependence, has not been studied. Although one literature source cited the “development of craving, tolerance, dependence, and withdrawal syndrome after the frequent consumption of high doses of MDPV”,¹ it is unclear how this conclusion was reached and does not appear to be scientifically or clinically grounded.

Evidence of possible physical dependence and tolerance building effects is indirect and can only be gleaned from case studies and unverified internet information reported by users. Penders and Gestring¹⁷ reported of a woman admitted to the psychiatric unit of a community hospital by way of an involuntary commitment initiated by her husband. The individual experienced fearful hallucinations of a home invasion that precipitated following daily use of MDPV for 2 weeks prior to admission. It is possible to infer that repeated and perhaps uncontrollable use of the drug is suggestive of physical dependence-like effects, however, this conclusion is highly speculative. Indication of possible tolerance is based on internet discussions documenting frequent redosing in a single session as well as using doses of over 200mg.¹ Although MDPV is reported to have a short duration of action, use of doses well over 6 times the typical 5 to 30 mg used in a single ingestion, suggests that users may develop tolerance to the drug's effects and thus possible physical dependence.

Conclusions

The abuse potential assessment of a drug should be based on a composite analysis of chemistry, pharmacology, clinical data, health risks that the drug presents, as well as ease of access to the drug and administration. The limited pharmacological data suggests that MDPV is similar to other synthetic cathinones, inhibiting reuptake and stimulating the release of dopamine and norepinephrine. This mechanism of action has been associated with the production of amphetamine-like effects and is supported by user reports of stimulant and mild psychoactive effects similar to those of amphetamine and MDMA. Further, as the drug's chemical structure allows it to be highly soluble and thus more easily cross the blood-brain barrier, a similar abuse liability profile to amphetamine may be expected. Taken together with the ease with which “bath

salts” can be purchased, numerous routes of administration and unconfirmed user accounts of short duration of action, there may be preliminary indication that MDPV is likely to be abused. However, in the absence of clinical studies, by relying solely on sparse pharmacological data and indirect evidence suggestive of abuse liability, it is not possible to make a definitive statement of abuse liability.

At present, there is no focused research on the dependence potential of MDPV and other synthetic cathinones. Sound scientific evidence that MDPV possesses dependence potential is not available. It is therefore not possible to conclude whether MDPV does or does not possess dependence potential.

References

1. Coppola M, Mondola R. 3,4-methylenedioxypropylone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett.* 2012;208(1):12-5.
2. Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol.* 2012;8(1):33-42.
3. Yohannan JC, Bozenko JS. The characterization of 3,4-methylenedioxypropylone. *Microgram Journal.* 2010;7:12-5.
4. Hassan NA, Gunaid AA, Murray-Lyon IM. Khat (*Catha edulis*): health aspects of khat chewing. *East Mediterr Health J.* 2007;13(3):706-18.
5. Centre for Disease Control and Prevention (CDC). Emergency department visits after the use of a drug sold as "bath salts". Michigan: 2011.
6. Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila).* 2011;49(6):499-505.
7. Meyer MR, Du P, Schuster F, Maurer HH. Studies on the metabolism of the alpha-pyrrolidinophenone designer drug methylenedioxy-propylone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high-resolution MS and its detectability in urine by GC-MS. *J Mass Spectrom.* 2010;45(12):1426-42.
8. Strano-Rossi S, Cadwallader AB, de la Torre X, Botre F. Toxicological determination and in vitro metabolism of the designer drug methylenedioxypropylone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom.* 2010;24(18):2706-14.
9. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin Syndrome Associated With MDPV Use: A Case Report. *Ann Emerg Med.* 2011.
10. Ojanpera IA, Heikman PK, Rasanen IJ. Urine analysis of 3,4-methylenedioxypropylone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit.* 2011;33(2):257-63.
11. Drug & Chemical Evaluation Section. 3,4-Methylenedioxypropylone (MDPV). US Drug Enforcement Administration, Control OoD; 2011.
12. Fuwa T., Fukumori N., Tanaka T., Kubo Y., Ogata A., Uehara S., et al. Microdialysis study of drug effects on central nervous system. Changes in dopamine levels in mice striatum after oral administration of methylenedioxypropylone [in Japanese]. *Tokyo-to Kenko Anzen Kenkyu Senta Kenkyu Nenpo.* 2007;58:287-92.
13. Fuwa T., Kodama T., Honda Y., Tanaka T., Kubo Y., Ohashi N., et al. Influence of Methylenedioxypropylone on Central Nervous System - Using Microdialysis Methods [in Japanese]. *ChemBio.* 2009;5:62-72.

14. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *J Med Chem.* 2006;49(4):1420-32.
15. Gough B, Imam SZ, Blough B, Slikker W, Jr., Ali SF. Comparative effects of substituted amphetamines (PMA, MDMA, and METH) on monoamines in rat caudate: a microdialysis study. *Ann N Y Acad Sci.* 2002;965:410-20.
16. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, et al. Energy-1 (NRG-1): don't believe what the newspapers say about it being legal. *Emerg Med J.* 2011;28(12):1068-70.
17. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: "Bath Salts". *Gen Hosp Psychiatry.* 2011;33(5):525-6.
18. Durham M. Ivory wave: the next mephedrone? *Emerg Med J.* 2011;28(12):1059-60.
19. Borek HA, Holstege CP. Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypropylpyrovalerone. *Ann Emerg Med.* 2012.
20. Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypropylpyrovalerone (MDPV). *J Med Toxicol.* 2012;8(1):69-75.
21. Kriikku P, Wilhelm L, Schwarz O, Rintatalo J. New designer drug of abuse: 3,4-Methylenedioxypropylpyrovalerone (MDPV). Findings from apprehended drivers in Finland. *Forensic Sci Int.* 2011;210(1-3):195-200.
22. Psychonaut Web Mapping Group. MDPV Report. London, United Kingdom: Institute of Psychiatry, Kings's College, 2010.

**For Your Approval: Revised MDPV Notice and Workplan**

Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-05-18 01:12 PM

Hi Jocelyn,

Please find attached, for your approval, revised versions of the MDPV Notice and Workplan, incorporating your comments of this morning.



NOI MDPV 2012-05-18.doc DRAFT MDPV WorkPlan May 18, 2012.doc

Please let me know if there's a good time this afternoon to discuss updating all workplans for next Wednesday, as per your note.

Thank you,

Tara
946-6521

141

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

*Notice to interested parties – Proposed amendment to Schedule III to the Controlled
Drugs and Substances Act*

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's intent to add 3,4-methylenedioxypropylvalerone (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule III to the *Controlled Drugs and Substances Act* (CDSA).

MDPV poses a potential risk to the health and safety of Canadians because its use can result in increased blood pressure and increased heart rate, and has also been associated with panic attacks, anxiety, hallucinations, suicidal thoughts and death.

Although MDPV is not listed in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have already elected to regulate it as a controlled substance including the United States, Australia, Denmark, Sweden and the United Kingdom.

Health Canada is not aware of any legitimate medical, scientific or industrial applications for MDPV and is therefore not intending to regulate MDPV in accordance with existing regulatory schemes under the CDSA.

This proposed action is in response to recent increases in law enforcement and border seizures of products labelled as "bath salts". Such products are not genuine bath salt products intended for softening/cleansing the skin, but contain one or more substances with stimulant properties including mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and MDPV. While the extent of their use in Canada is unknown, "bath salt" products are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky".

Including MDPV in Schedule III to the CDSA would prohibit the following activities with this substance: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The scheduling of MDPV will also ensure law enforcement can take action against all suspected illegal activities involving MDPV.

The publication of this notice begins a 60-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D, 123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email

at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. In particular, parties involved in legitimate activities involving MDPV are encouraged to respond to inform Health Canada's decision with respect to regulation of MDPV under the CDSA.

CATHY SABISTON

Director General

Controlled Substance and Tobacco Directorate

WORKPLAN: Scheduling of MDPV under the Controlled Drugs and Substances Act

Task/Activity		Target Date	Lead	Status
TRIAGE STATEMENT				
1	Draft triage statement	May 25, 2012	RPD	Ongoing
2	Consult with Treasury Board Secretariat	June 1, 2012	RPD, TBS	Ongoing
3	Obtain Director approval of triage statement	June 8, 2012	RPD, DO	
4	Obtain TBS approval of triage statement	June 15, 2012	RPD, DGO	
NOTICE TO INTERESTED PARTIES (Notice) - for publication in <i>Canada Gazette</i>, Part I				
1	Draft Notice	May 18, 2012	RPD	Ongoing
2	Obtain Director approval of Notice	May 25, 2012	RPD, DO	
3	Obtain DG, CSTD approval of Notice	June 1, 2012	RPD, DGO	
4	Brief senior management (ADM/DM) on Notice, as required	June 6, 2012	RPD, DGO, ADMO	
5	Submission to Canada Gazette Directorate	June 8, 2012 (minimum 6 working days prior to publication date)	RPD, Canada Gazette Directorate	
6	Publication in <i>Canada Gazette</i> , Part I	June 16, 2012	Canada Gazette Directorate	
7	60-day comment period ends	August 15, 2012	RPD	
8	Review and analysis of comments received	August 17, 2012	RPD	

ISSUE ANALYSIS SUMMARY				
1	Research & Analysis (including ORS contract on pharmacology)	July 6, 2012	RPD & ORS	Ongoing
2	Draft Issue Analysis Summary	July 27, 2012	RPD	Ongoing
3	Consultation with internal partners (DAS, ORS, etc.)	August	RPD	
4	Obtain Director, OCS approval of Issue Analysis Summary	August 31, 2012	RPD, DO	
REGULATORY PROPOSAL				
Note: Provided that no legitimate industry is identified via <i>Notice to interested parties</i>, there will be no administrative burden or compliance burden associated with proposal. Therefore, Regulatory Cost Calculator results will not be required.				
I. Preparation of Drafting Instructions				
1	Prepare drafting instructions	June 22, 2012	RPD	
2	Legal Services Review of drafting instructions	July 6, 2012	LSU	
3	Translate drafting instructions	July 13, 2012	RPD	
4	Obtain Director, OCS approval of drafting instructions	July 27, 2012	RPD, DO	
5	Obtain DG, CSTD approval of drafting instructions	August 10, 2012	RPD, DGO	
7	Submit drafting instructions to Department of Justice Drafting Service	August 17, 2012	RPD	

Page(s) 000652 to\à 000652

**Is(Are) exempted pursuant to section(s)
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**

143



Revised MDPV Workplan
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-05-22 04:25 PM

Hi Jocelyn,

I made two tiny revisions to this workplan, to reflect that the Notice is now with DO, OCS for approval.



DRAFT MDPV WorkPlan May 22, 2012.doc

Thank you,

Tara

WORKPLAN: Scheduling of MDPV under the *Controlled Drugs and Substances Act*

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s.21(1)(a)
s.21(1)(b)
000655

Page(s) 000656 to\à 000656

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est(sont) exemptée(s) en vertu de(s)(l')article(s)**

21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**

145

Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.
Jocelyn Kula to: Tara Phillips, Nathan Isotalo

2012-05-23 08:55 AM

Nathan- pls start on this right away.
For Tara's review by 12 pls.
Sent by blackberry
Johanne Beaulieu

----- Original Message -----

From: Johanne Beaulieu
Sent: 2012-05-23 08:02 AM EDT
To: Jocelyn Kula; Denis Arsenault; Tara Phillips
Cc: CSTD-OCS-DO
Subject: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.

Good Morning!

This one if for you.

Johanne
Andria Sherstone

----- Original Message -----

From: Andria Sherstone
Sent: 2012-05-23 07:35 AM EDT
To: CSTD-OCS-DO
Cc: SoniaH Lindblad1
Subject: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.

Please update QP to reflect this article.

Revised version to DGO COB today please.

Thanks!

-A

HC_Media_SC

----- Original Message -----

From: HC_Media_SC
Sent: 2012-05-23 07:25 AM EDT
Subject: CBC.ca/health - Dangerous drug catching on in rural N.S.

Distribution group/Groupe de distribution: Pharmaceuticals Biologics and Genetic Therapies -
HPFB/DGPSA, Controlled Substances - Substances contrôlées - HECSB/DGSESC,

CBC.ca/health
Dangerous drug catching on in rural N.S.
<http://www.cbc.ca/news/canada/nova-scotia/story/2012/05/22/ns-bath-salts-drugs.html>

Health officials in northern Nova Scotia are warning about a dangerous street drug that users may not even know they're taking.

The drug, known as "Bath Salts," is taken in powder form. It has the same effect as amphetamines, stimulants that speed up the central nervous system.

Dr. Heidi-Marie Farinholt of Aberdeen Hospital in Pictou County said the designer drug, with an

innocent-sounding name, is one of the most addictive drugs out there.

She said it kills and it's easy to buy online.

"It is extremely dangerous. So you take cocaine and multiply it by about a factor of 10 and you have this," Farinholt said.

"What we saw in Bangor when these things first came out they were so easy to get that the people who were pushing ~~Oxycontin, Percoset and Dilaudid on the street had to drop their prices and were a little bit~~ torqued that they were losing the market."

The negative effects of the drug include a dangerously elevated heart rate, paranoia, violent outbursts and hallucinations.

Greg Purvis, of Addiction Services at the Pictou Health Authority, told CBC News doctors at the Aberdeen Hospital are seeing two to three cases per week.

"Folks are ending up in the emergency room with hallucinations, delusions, psychosis, very bizarre behaviour, a lot of combativeness, a lot of agitation, a lot of aggression," he said.

He worries the drug will become more popular.

Officials say the drug is sometimes mixed with other drugs, such as marijuana.

"The user may not know what they are taking," Purvis said.

Dr. Robin Taylor, medical officer of health for those regions, said they've heard that "space weed," which is marijuana laced with the powder, is being sold to buyers who don't know what they're getting.

Purvis said some people may be fooled by the name and think they're taking a drug that is safe.

The drug is not the same as Epsom salts.

Bath Salts have been banned in the U.S. and several European countries but the drug is not currently regulated by Health Canada.

"I think it gives Health Canada the opportunity to look at this drug and get it on the controlled substances list, prior to it having similar impacts right across Canada," Purvis said.

Farinholt said she has seen the effects of violence and drugs but that Bath Salts are among the worst.

"My training was done Baltimore, Maryland which is one of the roughest places to work in the United States. Saw a lot of drugs, a lot of guns, and I have to say this drug scares me more than any of that ever did," she said.

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Merci.

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~~Consultez Newslink: nouveau site amélioré de la Surveillance des médias~~

146



CBC News Network - Nova Scotia officials warn over bath salts - May 23
2012, 9:45AM

HC_Media_SC to:
Sent by: Nicolas Frate
Bcc: Nathan Isotalo

2012-05-23 10:18 AM

Distribution group/Groupe de distribution: ~~Controlled Substances - Substances contrôlées -~~
HECSB/DGSESC, DComm,

CBC News Network
Wed May 23 2012
9:45 AM ET

Nova Scotia officials warn over bath salts

Suhana: IN NOVA SCOTIA HEALTH OFFICIALS ARE WARNING PEOPLE ABOUT A DANGEROUS STREET DRUG. IT'S KNOWN AS BATH SALTS AND IT MIGHT SOUND INNOCENT, BUT IT'S FAR FROM SAFE. THE EFFECTS IN FACT CAN BE TERRIFYING. THE DESIGNER DRUG IS KNOWN TO INDUCE PSYCHOTIC BEHAVIOUR LIKE PARANOIA AND HALLUCINATIONS. STEVE PUDDICOMBE HAS THE DETAILS.

YOU BASICALLY TAKE COCAINE, MULTIPLY IT BY A FACTOR OF TEN.

Reporter: THIS DOCTOR SAYS THE DESIGNER DRUG BATH SALT IS ONE OF THE MOST ADDICT ISSUE DRUGS OUT THERE. AND IT KILLS. AND IT'S EASY TO GET. RIGHT OFF OF INTERNET HEAD SHOPS.

WHAT WE SAW IN BANGER WHEN THE THINGS FIRST CAME OUT WAS IT WAS SO EASY TO GET THAT PEOPLE HAD TO DROP THEIR PRICES AND WERE TORCHED THAT THEY WERE LOSING THEIR MARKET BECAUSE THIS WAS SO EASY TO GET.

Reporter: IT'S NOT THE BIG CITIES THAT ARE BEING HIT BY THIS NEW DESIGNER DRUG. IT'S SMALL TOWNS LIKE NEW GLASGOW THAT ARE BEARING THE BRUNT OF ITS PAIN. WHAT'S ALARMING WITH THIS DRUG IS THE SIDE EFFECTS. THE EXPERTS ARE SEEING IN TWO TO THREE CASES AT THE ABERDEEN HOSPITAL IN PICTOU COUNTY EACH WEEK.

FOLKS ARE ENDING UP IN EMERGENCY LOOMS AGGRESSION.

Reporter: BATH SALTS HAVE BEEN BANNED IN THE U.S. AND SEVERAL EUROPEAN COUNTRIES BUT NOT IN CANADA YET.

I THINK IT GIVES HEALTH CANADA AN OPPORTUNITY TO LOOK AT THIS DRUG AND GET IT ON THE CONTROLLED SUBSTANCE LIST PRIOR TO IT HAVING SIMILAR IMPACTS RIGHT ACROSS CANADA.

Reporter: THE DOCTOR SAYS SOMETHING HAS TO BE DONE SOON OR THERE WILL BE DIRE CONSEQUENCES.

MY TRAINING WAS DONE DOWN IN BALTIMORE, MARYLAND WHICH IS ONE OF THE ROUGHEST PLACES TO WORK IN THE UNITED STATES. SAW A LOT OF DRUGS, A LOT OF GUNS. AND I HAVE TO SAY THIS DRUG SCARES ME MORE THAN ANY OF THAT EVER DID.

Reporter: STEPHEN PUDDICOMBE, CBC NEWS, NEW GLASGOW.

-END-

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Thank you.

000660

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Merci.

L'Équipe de surveillance des médias

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Consultez Newslink: nouveau site amélioré de la Surveillance des médias

147



For Your Review: Updated Bath Salts QP Note
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-05-23 11:56 AM

Hi Jocelyn,

Here is the link to the updated QP Note on bath salts, for your review.



I've left a hardcopy with Ian as well as supporting documents.

Thank you,

Tara

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-23 11:50 AM -----

From: Jocelyn Kula/HC-SC/GC/CA
To: "Tara Phillips" <tara.phillips@hc-sc.gc.ca>, "Nathan Isotalo" <nathan.isotalo@hc-sc.gc.ca>
Date: 2012-05-23 08:55 AM
Subject: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.

Nathan- pls start on this right away.

For Tara's review by 12 pls.

Sent by blackberry

Johanne Beaulieu

----- Original Message -----

From: Johanne Beaulieu
Sent: 2012-05-23 08:02 AM EDT
To: Jocelyn Kula; Denis Arsenault; Tara Phillips
Cc: CSTD-OCS-DO
Subject: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.

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From: Andria Sherstone
Sent: 2012-05-23 07:35 AM EDT
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Cc: SoniaH Lindblad1
Subject: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.

Please update QP to reflect this article.

Revised version to DGO COB today please.

Thanks!

-A

HC_Media_SC

000662

QUESTION PERIOD NOTE
NOTE POUR LA PÉRIODE DE
QUESTIONS

Date:	May 23, 2012
Classification :	HECS PROTECTED - SESC PROTÉGÉ

English:

MDPV IN BATH SALTS

SYNOPSIS - SOMMAIRE

English:

Health officials in northern Nova Scotia have issued a warning concerning the dangers posed by an emerging street drug known as "bath salts". On May 22, 2012, CBC reported on the increasing prevalence of the drug in northern Nova Scotia, adding to the recent media attention surrounding the use of "bath salts". "Bath salts" may contain a mixture of MDPV (3,4-methylenedioxypropylone), methylone and/or mephedrone. Such products are likely labelled as "bath salts" in order to appear legal. Both methylone and mephedrone are considered controlled substances in Canada, while MDPV is not yet included in one of the Schedules to the Controlled Drugs and Substances Act (CDSA). Canadian law enforcement and border services are seeing an increasing trend in the incidence of "bath salts" seizures.

ANTICIPATED QUESTION - QUESTION PRÉVUE

English:

What is the Government doing about MDPV in bath salts?

English:

- This Government is very concerned about the public health and safety risks associated with the use of "bath salts". ~~the recent drug analyses and seizures of so-called "bath salts" containing a substance called MDPV.~~
- Health Canada is assessing MDPV, a key ingredient in "bath salts", for scheduling under the *Controlled Drugs and Substances Act*. ~~Health Canada will be working with law enforcement agencies to determine the most appropriate next steps to address the public health and safety risks associated with the use of MDPV.~~
- This Government is committed to controlling substances that produce harm to health and to society when abused.

Français:

BACKGROUND - CONTEXTE

English:

A number of recent media articles in both the United States and Canada have highlighted dangers posed by products labelled and marketed as "bath salts" which are being used as amphetamine-like stimulants. These products are not genuine bath salt products at all, which are typically composed of water soluble mineral salts and are added to water for the purpose of cleansing, softening and/or perfuming the skin.

Canadian media reports have originated primarily from Eastern provinces, including New Brunswick and Nova Scotia. On May 18, 2012, health officials in northern Nova Scotia issued a warning concerning the dangers posed by "bath salts", including reports of cases where use has resulted in the user requiring emergency care.

~~Preliminary reports indicate that~~ The psychoactive ingredients contained in "bath salts" products may include mephedrone, methylone and/or MDPV (3,4-methylenedioxypropylone). In addition, there have been reports of "bath salts" being used to lace other drugs such as marijuana.

Mephedrone and methylone are analogues of amphetamine and is thus considered to be included in Item 1 of

Schedule III to the CDSA. ~~Adverse effects associated with the use of amphetamines can include seizures, cerebral hemorrhage, high fever, coma or death.~~

MDPV is a central nervous system stimulant. Adverse physical effects associated with the use of stimulants can include palpitations, irregular or abnormal heartbeat, heart attack or cardiovascular collapse. MDPV use has also been associated with severe panic attacks and anxiety, as well as hallucinations and psychosis. ~~whose use can cause increased blood pressure and increased heart rate. The use of MDPV has also been associated with panic attacks, anxiety and hallucinations, suicidal thoughts, tendencies and death.~~ MDPV is not regulated as a controlled substance in Canada.

~~From other analyses, from January 2010 to present, Health Canada's Drug Analysis Service (DAS) has identified MDPV or mephedrone in 461332 exhibits of suspected controlled substances seized by law enforcement. 444345 of these exhibits were found to contain MDPV alone. Only 17 were found to contain mephedrone.~~

The CDSA prohibits all activities, e.g., possession, production, distribution, sale, import, and/or export, involving substances listed in one of the Schedules to the Act, unless authorized by regulation. Health Canada considers several factors in determining whether the scheduling of a substance under the Controlled Drugs and Substances Act (CDSA) is warranted. These include:

- Overall risk to public health and safety posed by the substance.
- Chemical and pharmacological similarity to other substances already regulated under the CDSA;
- Legitimate uses of the substance (i.e., therapeutic, industrial or commercial);
- Potential for abuse and risk of addiction associated with the substance;
- Extent of actual abuse of the substance in Canada and internationally; and
- International requirements and trends in international control.

In the United States, the Drug Enforcement Administration has recently used its emergency scheduling authority to temporarily ban mephedrone, MDPV and methyldone. MDPV has also recently been banned in the United Kingdom.

No drug products containing MDPV or mephedrone have been approved for sale in Canada.

~~Health Canada will continue to work with law enforcement agencies in determining the most appropriate next steps in addressing the public health and safety risks associated with the use of MDPV.~~

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

Contact/Personne ressource : Jocelyn Kula/HC-SC/GC/CA	Tel. no./No de tél. 946-0125	Approved by/ Approuvé par Hilary Geller, ADM (HECS/SESC)	Tel. no./No. de tél. 946-6701
	Mobile/ Cellulaire:	Title/ Titre:	Mobile/ Cellulaire:
Alternate/ Secondaire:	Telephone/ Téléphone:		
	Mobile/ Cellulaire:		

Date Prepared/Préparé le : 2012-05-23

Prepared by/Préparé par : Nathan Isotalo **Phone/ No de tél. :** 613-941-1511

Office/Bureau : CSTD - Office of Controlled Substances

**Date Contact Signed/
Signature de la personne
ressource :**

Contact Signed - Signé

**D.G. Verification/
Vérification par le D.E. :**

Cathy Sabiston

D.G. Approved / Approuvé D.E.

**Date D.G. Verified/
Date vérifié par le D.E. :**

Programme : Controlled Substances and Tobacco Directorate

**ADM Approved/ Approbation
par le SMA :** Hilary Geller, ADM (HECS/SESC)
(946-6701)

Branch/ Direction générale : HECS/SESC

Department/ Ministère : Health Canada / Santé Canada

149

----- Original Message -----

From: HC_Media_SC

Sent: 2012-05-23 07:25 AM EDT

Subject: CBC.ca/health - Dangerous drug catching on in rural N.S.

Distribution group/Groupe de distribution: Pharmaceuticals Biologics and Genetic Therapies - HPFBD/DGPDA, Controlled Substances - Substances contrôlées - HECSB/DGSESC,

CBC.ca/health

Dangerous drug catching on in rural N.S.

<http://www.cbc.ca/news/canada/nova-scotia/story/2012/05/22/ns-bath-salts-drugs.html>

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She said it kills and it's easy to buy online.

"It is extremely dangerous. So you take cocaine and multiply it by about a factor of 10 and you have this," Farinholt said.

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Officials say the drug is sometimes mixed with other drugs, such as marijuana.

"The user may not know what they are taking," Purvis said.

Dr. Robin Taylor, medical officer of health for those regions, said they've heard that "space weed," which is marijuana laced with the powder, is being sold to buyers who don't know what they're getting.

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Thank you.

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Merci.

L'Équipe de surveillance des médias
HC/SC - PHAC/ASPC

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Consultez Newslink: nouveau site amélioré de la Surveillance des médias

150



Request for Updated Stats on MDPV
Tara Phillips to: Guy Aucoin
Cc: Nathan Isotalo

2012-05-23 03:11 PM

Hi Guy,

We have been asked to update our QP Note on MDPV and would like to update the following statement from the previous version:

From January 2010 to present, Health Canada's Drug Analysis Service (DAS) has identified MDPV or mephedrone in 332 exhibits of suspected controlled substances seized by law enforcement. 315 of these exhibits were found to contain MDPV alone. Only 17 were found to contain mephedrone.

Would you be able to provide us with updated numbers?

Unfortunately, the deadline for us to submit the revised document to our DG is close of business today.

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

151



Fw: For Your Review: Revised QP Note on MDPV in "Bath Salts"

Tara Phillips to: Nathan Isotalo

2012-05-23 03:16 PM

Meant to copy you on message below.

Tara

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-23 03:15 PM -----

From: Tara Phillips/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-05-23 03:15 PM
Subject: For Your Review: Revised QP Note on MDPV in "Bath Salts"

Hi Jocelyn,

I have incorporated your comments and attached the link.



The one outstanding issue is to update the DAS numbers in the Background section. I spoke to Guy Aucoin but he is in a meeting and I don't expect he can get updated numbers to us today.

Thank you,

Tara

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-23 03:13 PM -----

From: Johanne Beaulieu/HC-SC/GC/CA
To: "Kula, Jocelyn" <jocelyn.kula@hc-sc.gc.ca>, "Arsenault, Denis" <denis.arsenault@hc-sc.gc.ca>, "Phillips, Tara" <tara.phillips@hc-sc.gc.ca>
Cc: CSTD-OCS-DO
Date: 2012-05-23 08:02 AM
Subject: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.

Good Morning!

This one if for you.

Johanne
Andria Sherstone

----- Original Message -----

From: Andria Sherstone
Sent: 2012-05-23 07:35 AM EDT
To: CSTD-OCS-DO
Cc: SoniaH Lindblad1
Subject: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.

Please update QP to reflect this article.

Revised version to DGO COB today please.

Thanks!

000670

-A

HC_Media_SC

----- Original Message -----

From: HC Media SC

Sent: 2012-05-23 07:25 AM EDT

Subject: CBC.ca/health - Dangerous drug catching on in rural N.S.

Distribution group/Groupe de distribution: Pharmaceuticals Biologics and Genetic Therapies -
HPFB/DGPSA, Controlled Substances - Substances contrôlées - HECSB/DGSESC,

CBC.ca/health

Dangerous drug catching on in rural N.S.

<http://www.cbc.ca/news/canada/nova-scotia/story/2012/05/22/ns-bath-salts-drugs.html>

Health officials in northern Nova Scotia are warning about a dangerous street drug that users may not even know they're taking.

The drug, known as "Bath Salts," is taken in powder form. It has the same effect as amphetamines, stimulants that speed up the central nervous system.

Dr. Heidi-Marie Farinholt of Aberdeen Hospital in Pictou County said the designer drug, with an innocent-sounding name, is one of the most addictive drugs out there.

She said it kills and it's easy to buy online.

"It is extremely dangerous. So you take cocaine and multiply it by about a factor of 10 and you have this," Farinholt said.

"What we saw in Bangor when these things first came out they were so easy to get that the people who were pushing Oxycontin, Percoset and Dilaudid on the street had to drop their prices and were a little bit torqued that they were losing the market."

The negative effects of the drug include a dangerously elevated heart rate, paranoia, violent outbursts and hallucinations.

Greg Purvis, of Addiction Services at the Pictou Health Authority, told CBC News doctors at the Aberdeen Hospital are seeing two to three cases per week.

"Folks are ending up in the emergency room with hallucinations, delusions, psychosis, very bizarre behaviour, a lot of combativeness, a lot of agitation, a lot of aggression," he said.

He worries the drug will become more popular.

Officials say the drug is sometimes mixed with other drugs, such as marijuana.

"The user may not know what they are taking," Purvis said.

Dr. Robin Taylor, medical officer of health for those regions, said they've heard that "space weed," which is marijuana laced with the powder, is being sold to buyers who don't know what they're getting.

Purvis said some people may be fooled by the name and think they're taking a drug that is safe.

The drug is not the same as Epsom salts.

Bath Salts have been banned in the U.S. and several European countries but the drug is not currently regulated by Health Canada.

"I think it gives Health Canada the opportunity to look at this drug and get it on the controlled substances list, prior to it having similar impacts right across Canada," Purvis said.

Farinholt said she has seen the effects of violence and drugs but that Bath Salts are among the worst.

~~"My training was done in Baltimore, Maryland which is one of the roughest places to work in the United States. Saw a lot of drugs, a lot of guns, and I have to say this drug scares me more than any of that ever did," she said.~~

You are receiving this e-mail because you are subscribed to the distribution group identified at the top of this e-mail message. If you wish to unsubscribe from this group, please reply to this message or send a request to HC_Media_SC@hc-sc.gc.ca

Thank you.

Media Monitoring Team
HC/SC - PHAC/ASPC

Vous recevez ce courriel parce que vous faites partie du groupe de distribution qui apparaît en haut du présent courriel. Si vous désirez que votre nom soit retiré de ce groupe, veuillez répondre à ce courriel et demander que votre nom soit retiré ou envoyer une demande à HC_Media_SC@hc-sc.gc.ca

Merci.

L'Équipe de surveillance des médias
HC/SC - PHAC/ASPC

Check out Newslink: Media Monitoring's new and improved web presence
Consultez Newslink: nouveau site amélioré de la Surveillance des médias

152



For your review: MDPV Notice Translation
Tara Phillips to: Nathan Isotalo

2012-05-23 03:48 PM

History: This message has been replied to.

Hi Nathan,

~~Could you please review the attached translation and submit any comments to me by noon tomorrow?~~

The translation was based on this version of the Notice:



NOI MDPV 2012-05-18.doc

Thank you,

Tara

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-23 03:46 PM -----

From: Ian McGillivray/HC-SC/GC/CA
To: , Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-23 03:45 PM
Subject: Please review '8416614_FR_NOI_MDPV_2012_05_18[1]'

Please review the attached document.

Ian McGillivray

Regulatory Policy Division/Division des politiques réglementaires
Office of Controlled Substances/Bureau des substances contrôlées
Health Canada/Santé Canada
Tel: (613)-960-6069 Fax/Telecopieur: (613)-946-4224
E-Mail/Courriel: ian.mcgillivray@hc-sc.gc.ca



- 8416614_FR_NOI_MDPV_2012_05_18[1].doc

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

*Notice to interested parties – Proposed amendment to Schedule III to the Controlled
Drugs and Substances Act*

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's intent to add 3,4-methylenedioxypropylvalerone (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule III to the *Controlled Drugs and Substances Act* (CDSA).

MDPV poses a potential risk to the health and safety of Canadians because its use can result in increased blood pressure and increased heart rate, and has also been associated with panic attacks, anxiety, hallucinations, suicidal thoughts and death.

Although MDPV is not listed in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have already elected to regulate it as a controlled substance including the United States, Australia, Denmark, Sweden and the United Kingdom.

Health Canada is not aware of any legitimate medical, scientific or industrial applications for MDPV and is therefore not intending to regulate MDPV in accordance with existing regulatory schemes under the CDSA.

This proposed action is in response to recent increases in law enforcement and border seizures of products labelled as "bath salts". Such products are not genuine bath salt products intended for softening/cleansing the skin, but contain one or more substances with stimulant properties including mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and MDPV. While the extent of their use in Canada is unknown, "bath salt" products are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky".

Including MDPV in Schedule III to the CDSA would prohibit the following activities with this substance: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The scheduling of MDPV will also ensure law enforcement can take action against all suspected illegal activities involving MDPV.

The publication of this notice begins a 60-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D, 123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email

at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. In particular, parties involved in legitimate activities involving MDPV are encouraged to respond to inform Health Canada's decision with respect to regulation of MDPV under the CDSA.

CATHY SABISTON

Director General

Controlled Substance and Tobacco Directorate

MINISTÈRE DE LA SANTÉ

LOI RÉGLEMENTANT CERTAINES DROGUES ET AUTRES SUBSTANCES

Avis aux intéressés – Modification proposée de l'annexe III de la Loi réglementant certaines drogues et autres substances

Le présent avis fournit aux intéressés l'occasion de formuler des commentaires sur la proposition de Santé Canada d'ajouter la 3,4-méthylènedioxyprovalérone (MDPV), ses sels, ses dérivés, ses isomères et ses analogues ainsi que les sels de ses dérivés, isomères et analogues à l'annexe III de la *Loi réglementant certaines drogues et autres substances* (LRCDas).

La MDPV présente un risque pour la santé et la sécurité des Canadiens. Outre le risque d'augmentation de la pression artérielle et du rythme cardiaque, la consommation de MDPV a été associée à des crises de panique, de l'anxiété, des hallucinations, des pensées suicidaires et des décès.

Bien que cette substance ne soit visée par aucune convention des Nations Unies sur le contrôle des drogues, un certain nombre de pays, dont les États-Unis, l'Australie, le Danemark, la Suède et le Royaume-Uni, ont déjà choisi de la réglementer en tant que substance contrôlée.

Santé Canada ne connaît aucune utilisation médicale, scientifique ou industrielle légitime de la MDPV et ne compte par conséquent pas réglementer cette substance conformément aux systèmes de réglementation en place en vertu de la LRCDas.

La mesure proposée s'explique par la hausse récente du nombre de saisies policières et aux frontières de produits étiquetés comme « sels de bain ». Contrairement aux sels de bain ordinaires qui sont destinés à adoucir et à nettoyer la peau, ces produits contiennent une ou plusieurs substances ayant des propriétés stimulantes, comme la méphédronne et la méthylone (qui figurent déjà à l'annexe III de la LRCDas en tant qu'analogues de l'amphétamine) ainsi que la MDPV. Bien que la mesure dans laquelle ils sont utilisés au Canada demeure inconnue, ces « sels de bain » sont vendus sur Internet et dans des boutiques spécialisées. Les mentions « engrais pour plantes » et « non destiné à la consommation humaine » peuvent également figurer sur l'étiquette de ces produits, qui sont vendus sous différents noms, dont MITSEEZ, MOJO Novelty Bath Salts, Ivory Snow, Purple Wave et Vanilla Sky.

L'inscription de la MDPV à l'annexe III de la LRCDas permettrait d'interdire les activités suivantes liées à cette substance : la possession, le trafic, la possession en vue d'en faire le trafic, l'importation, l'exportation, la possession aux fins d'exportation et la production. L'ajout de la MDPV à l'annexe permettrait également aux organismes d'exécution de la loi de prendre des mesures en cas d'activités illégales soupçonnées avec cette substance.

La publication du présent avis marque le début d'une période de commentaires de 60 jours. Si vous êtes intéressé par le processus ou que vous voulez formuler des commentaires sur cet avis, veuillez communiquer avec M. Nathan Isotalo, Division des politiques et de la réglementation, Bureau des substances contrôlées, 3503D-123, rue Slater, Ottawa (Ontario), Canada K1A 0K9, par télécopieur au 613-946-4224 ou par courriel à OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. Les personnes qui exercent des activités légitimes avec la MDPV sont invitées plus particulièrement à commenter la décision de Santé Canada de régir la MDPV aux termes de la LRCDAS.

CATHY SABISTON
Directrice générale
Direction des substances contrôlées et de la lutte au
tabagisme

154



Fw: MDPV QP Note with DAS Numbers Updated
Tara Phillips to: Nathan Isotalo

2012-05-23 05:04 PM

FYI.

T

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-23 05:04 PM -----

From: Jocelyn Kula/HC-SC/GC/CA
To: Johanne Beaulieu/HC-SC/GC/CA@HWC
Cc: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-23 04:57 PM
Subject: MDPV QP Note with DAS Numbers Updated

For your review. DAS got back to us sooner than expected!

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224

----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2012-05-23 04:57 PM -----

From: Tara Phillips/HC-SC/GC/CA
To: Jocelyn Kula/HC-SC/GC/CA@HWC
Date: 2012-05-23 04:56 PM
Subject: MDPV QP Note: (Re: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.)

Hi Jocelyn,

The updated numbers from DAS have now been inserted in the Background section.



Thank you,

Tara

Jocelyn Kula Hi Johanne As requested, please find attached... 2012-05-23 04:02:48 PM

From: Jocelyn Kula/HC-SC/GC/CA
To: Johanne Beaulieu/HC-SC/GC/CA@HWC
Cc: CSTD-OCS-DO, Tara Phillips/HC-SC/GC/CA@HWC, Mélanie Séguin/HC-SC/GC/CA@HWC
Date: 2012-05-23 04:02 PM
Subject: Re: Fw: CBC.ca/health - Dangerous drug catching on in rural N.S.

Hi Johanne

As requested, please find attached updated QP note on MDPV.



Note that we are still missing updated numbers from DAS for the Background section. We are waiting to hear back from Guy Aucoin.

Jocelyn

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224

Johanne Beaulieu Good Morning! This one if for you.

2012-05-23 08:02:17 AM



Fw: URGENT: MO Request - Bath Salts
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-05-24 09:53 AM

Hi Jocelyn,

Please see responses below, for your review.

1. A brief explanation of what bath salts are and what their ingredients are.

Over the past several months, there has been growing interest in and media reports of synthetic stimulants sold under the guise of "bath salts". In Canada, law enforcement and border seizures of products labelled as "bath salts" have been increasing. Such products are not genuine bath salt products, i.e., Epsom salts, intended for softening/cleansing the skin, but contain one or more substances with stimulant properties such as mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and 3,4-methylenedioxypyrovalerone (MDPV). MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities, with oral ingestion, injection, and nasal insufflation (snorting) being most prevalent. While the extent of their use in Canada is unknown, "bath salts" are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption" to circumvent regulatory control and drug abuse legislation. As such, they are considered "legal highs". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky".

2. How seizure data has indicated that MDPV only bath salts are becoming more prevalent.

From January 2010 to present, Health Canada's Drug Analysis Service (DAS) has identified MDPV or mephedrone in 461 exhibits of suspected controlled substances seized by law enforcement. 444 of these exhibits were found to contain MDPV and 17 were found to contain mephedrone.

3. HC has acted on the data by initiating work to schedule (break down the work in progress e.g. Triage questionnaire, pharmacology assessment, etc. and associated timelines)

Health Canada has prepared a *Notice to interested parties* to be published in *Canada Gazette*, Part I in June 2012. The Notice will provide interested stakeholders with a 60-day opportunity to provide comments on Health Canada's intent to add MDPV to Schedule III to the *Controlled Drugs and Substances Act* (CDSA).

As part of its scheduling assessment, Health Canada commissioned an Abuse Liability and Dependence Potential Assessment, which has been completed. The full scheduling assessment is underway.

s.21(1)(a)

s.21(1)(b)

5. Please add in any other details you think would be useful.

Canadian media reports have originated primarily from Eastern provinces, including New Brunswick and Nova Scotia. On May 18, 2012, health officials in northern Nova Scotia issued a warning concerning the dangers posed by "bath salts", including reports of cases where use has resulted in the user requiring emergency care.

Thank you,

Tara

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-24 09:03 AM -----

From: Jocelyn Kula/HC-SC/GC/CA
To: "Tara Phillips" <tara.phillips@hc-sc.gc.ca>
Date: 2012-05-24 08:59 AM
Subject: Fw: URGENT: MO Request - Bath Salts

Here is the request. We need a draft for 10 am pls.

JK

Sent by blackberry

Johanne Beaulieu

----- Original Message -----

From: Johanne Beaulieu
Sent: 2012-05-24 08:37 AM EDT
To: Denis Arsenault; Tara Phillips
Cc: Jocelyn Kula
Subject: Fw: URGENT: MO Request - Bath Salts

Johanne Beaulieu

----- Original Message -----

From: Johanne Beaulieu
Sent: 2012-05-24 08:36 AM EDT
To: Jocelyn Kula
Subject: Fw: URGENT: MO Request - Bath Salts

Good Morning Jocelyn!

Please confirm that you are working on this response.

Thanks.

Johanne

Andria Sherstone

----- Original Message -----

From: Andria Sherstone
Sent: 2012-05-24 08:29 AM EDT
To: Johanne Beaulieu; Jocelyn Kula
Cc: CSTD-DGO; CSTD-OCS-DO

s.21(1)(a)

s.21(1)(b)

Subject: URGENT: MO Request - Bath Salts
Please see the request from MO below.

Please prepare a response to the Qs below in e-mail format.

This is required in DGO no later than 1130 today.

At the same time, please route up the revised bath salts QP requested yesterday, if it has already not
been done.

Thanks!

-A

Ian Hobler

----- Original Message -----

From: Ian Hobler

Sent: 2012-05-24 08:14 AM EDT

To: Andria Sherstone

Subject: MO Request - Bath Salts

Hi Andria.

MO has asked for an update on OCS's work on bath salts (MDPV specifically) for today.

Could I please get by mid-afternoon:

1. A brief explanation of what bath salts are and what their ingredients are.
2. How seizure data has indicated that MDPV only bath salts are becoming more prevalent.
3. HC has acted on the data by initiating work to schedule (break down the work in progress e.g. Triage questionnaire, pharmacology assessment, etc. and associated timelines)

5. Please add in any other details you think would be useful.

I think we can avoid a fully-blown BN to MO if we get this up in time. Please note this is for MO's info on the policy side, not for communication to the public - media lines are still good for that.

Give me a call if you would like to discuss.

Thanks!

Ian

156



Re: Fw: URGENT: MO Request - Bath Salts 
Jocelyn Kula to: Johanne Beaulieu
Cc: Tara Phillips, Nathan Isotalo

2012-05-24 10:07 AM

For your approval. I am on my way to Delsys now.

1. A brief explanation of what bath salts are and what their ingredients are.

Over the past several months, there have been increasing media reports that synthetic stimulants sold under the guise of "bath salts" are appearing in Canada. Law enforcement and border seizures of products labelled as "bath salts" have also been increasing. Such products are not genuine bath salt products, i.e., epsom salts, intended for softening/cleansing the skin, but contain one or more substances with stimulant properties such as mephedrone and methyone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and 3,4-methylenedioxypropylvalerone (MDPV). MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities, with oral ingestion, injection, and nasal insufflation (snorting) being most prevalent. While the extent of their use in Canada is unknown, "bath salts" are available for purchase on the Internet and may be found in alternative lifestyle stores. Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky". These products may also be labelled as "plant food" and/or "not for human consumption" to circumvent regulatory control.

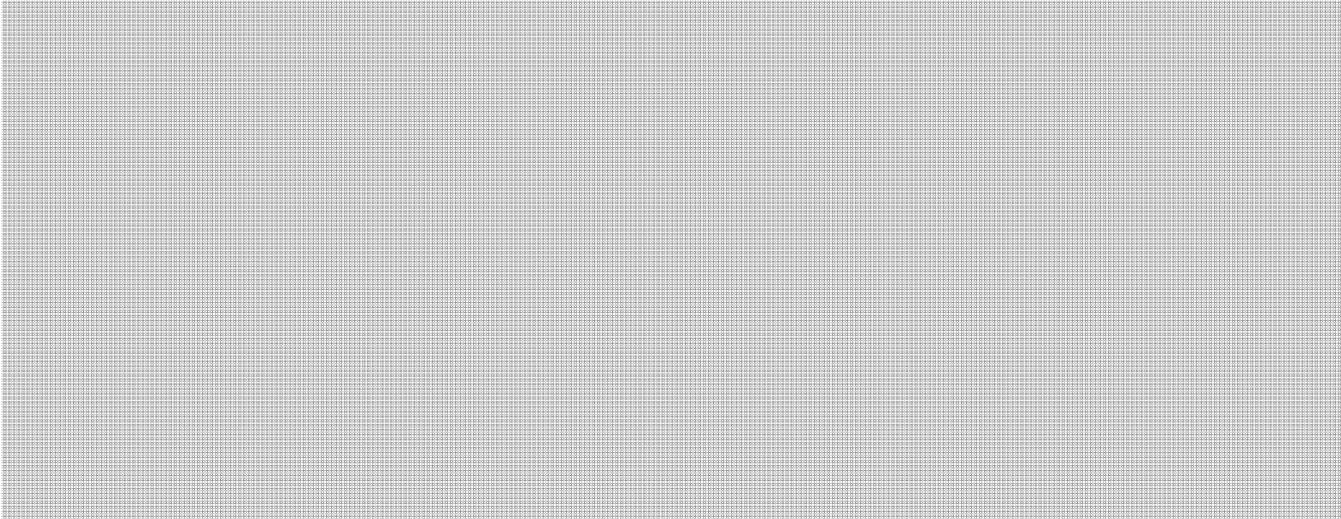
2. How seizure data has indicated that MDPV only bath salts are becoming more prevalent.

From January 2010 to present, Health Canada's Drug Analysis Service (DAS) has identified MDPV or mephedrone in 461 exhibits of suspected controlled substances seized by law enforcement. 444 of these exhibits were found to contain MDPV and 17 were found to contain mephedrone.

3. HC has acted on the data by initiating work to schedule (break down the work in progress e.g. Triage questionnaire, pharmacology assessment, etc. and associated timelines)

Controlled Substances and Tobacco Directorate (CSTD) has prepared a *Notice to Interested Parties*, and is intending to publish this in *Canada Gazette*, Part I in June 2012. The Notice will provide interested stakeholders with a 60-day opportunity to provide comments on Health Canada's intent to add MDPV to Schedule III to the *Controlled Drugs and Substances Act* (CDSA).

As part of its scheduling assessment, Health Canada let an external contract aimed at assessing the abuse liability and dependence potential of MDPV. The assessment was completed in May, and a comprehensive scheduling assessment is now underway with a target timeline of August 2012.



5. Please add in any other details you think would be useful.

Canadian media reports have originated primarily from Eastern provinces, including New Brunswick and Nova Scotia. On May 18, 2012, health officials in northern Nova Scotia issued a warning concerning the dangers posed by "bath salts", including reports of cases where use has resulted in the user requiring emergency care.

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224

Johanne Beaulieu Good Morning Jocelyn! Please confirm that you... 2012-05-24 08:36:32 AM

From: Johanne Beaulieu/HC-SC/GC/CA
To: "Kula, Jocelyn" <jocelyn.kula@hc-sc.gc.ca>
Date: 2012-05-24 08:36 AM
Subject: Fw: URGENT: MO Request - Bath Salts

Good Morning Jocelyn!

Please confirm that you are working on this response.

Thanks.

Johanne
Andria Sherstone

----- Original Message -----

From: Andria Sherstone
Sent: 2012-05-24 08:29 AM EDT
To: Johanne Beaulieu; Jocelyn Kula
Cc: CSTD-DGO; CSTD-OCS-DO
Subject: URGENT: MO Request - Bath Salts

Please see the request from MO below.

Please prepare a response to the Qs below in e-mail format.

This is required in DGO no later than 1130 today.

At the same time, please route up the revised bath salts QP requested yesterday, if it has already not been done.

Thanks!

-A

Ian Hobler

157



Fw: MDPV - Revisions required
Tara Phillips to: Nathan Isotalo

2012-05-24 03:30 PM

for the file

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-24 03:29 PM -----

From: Jocelyn Kula/HC-SC/GC/CA
To: Andria Sherstone/HC-SC/GC/CA@HWC
Cc: Johanne Beaulieu/HC-SC/GC/CA@HWC, Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-24 03:06 PM
Subject: Re: MDPV - Revisions required

Hi Andria,

Here are responses to Cathy's comments and questions.

1. A brief explanation of what bath salts are and what their ingredients are.

Over the past several months, there have been increasing media reports on synthetic stimulants sold under the guise of "bath salts" appearing in Canada. Law enforcement and border seizures of products labelled as "bath salts" have also been increasing. Such products are not genuine bath salt products, i.e., epsom salts, intended for softening/cleansing the skin, but contain one or more substances with stimulant properties such as mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and 3,4-methylenedioxypropylone (MDPV). MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities, with oral ingestion, injection, and nasal insufflation (snorting) being most prevalent. While the extent of their use in Canada is unknown, "bath salts" are available for purchase on the Internet and may be found in alternative lifestyle stores. Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky". These products may also be labelled as "plant food" and/or "not for human consumption" to circumvent regulatory control.

CAS comment - do all Bath Salts contain all 3 ingredients (MDPV, Mephedrone, Methylone)? Please clarify.

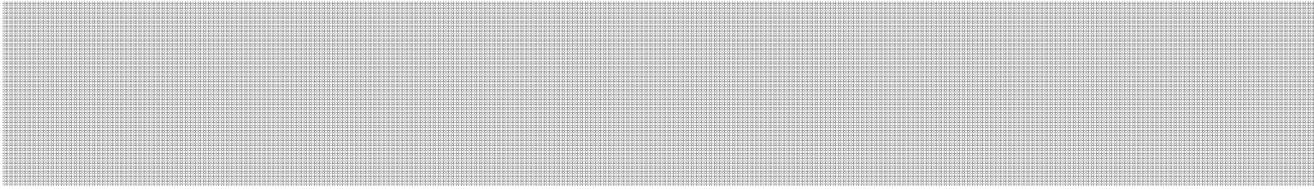
No. "Bath salts" contain one or more substances with stimulant properties such as MDPV, mephedrone and/or methylone but not necessarily all three. In fact, DAS analysis has not yet identified both MDPV and mephedrone in the same exhibit and has not yet identified methylone in any exhibits. Methylone has however been identified in "bath salt" products in the United States. [Note, that we have now underlined the text "...contain one or more substances....."; feel free to remove if you don't think this is necessary for ADMO]

2. How seizure data has indicated that MDPV only bath salts are becoming more prevalent.

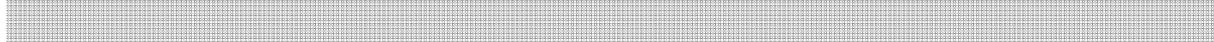
From January 2010 to present, Health Canada's Drug Analysis Service (DAS) has identified MDPV or mephedrone in 461 exhibits of suspected controlled substances seized by law enforcement. 444 of these exhibits were found to contain MDPV and 17 were found to contain mephedrone.

CAS comment - what about MDPV alone? None of the 444 exhibits identified as MDPV contained mephedrone, and none of the 17 exhibits identified as mephedrone contained MDPV. The reason we did not use the word 'alone' with the MDPV number is because DAS cannot be certain that no other controlled substances were present in the sample.

3. HC has acted on the data by initiating work to schedule (break down the work in progress e.g. Triage questionnaire, pharmacology assessment, etc. and associated timelines)

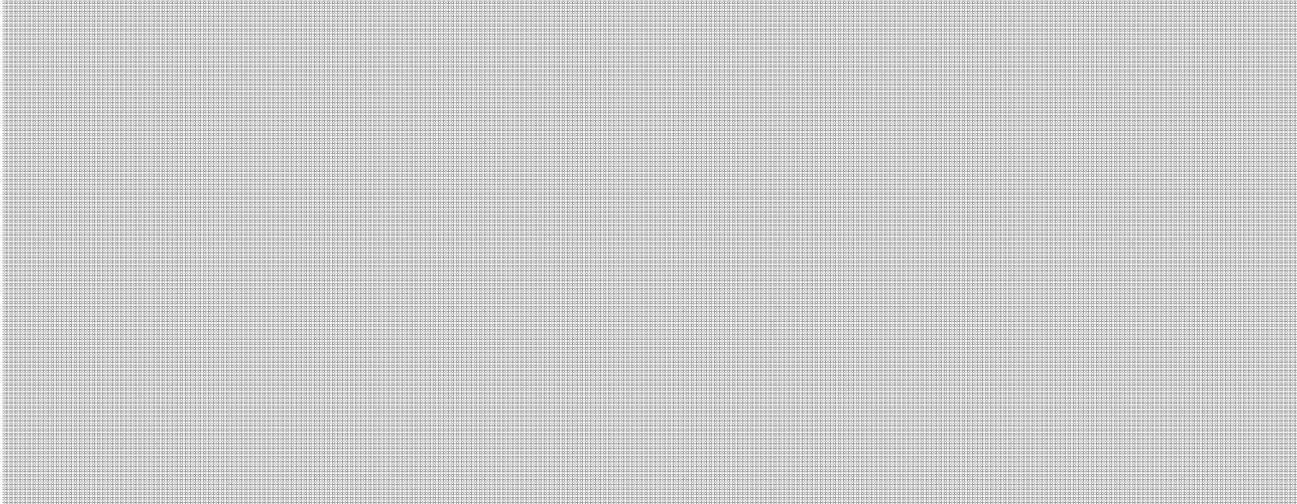


As part of its scheduling assessment, Health Canada let an external contract aimed at assessing the abuse liability and dependence potential of MDPV. The assessment was completed in May 2012, and concluded that based on MDPV's chemical structure, a similar abuse liability to amphetamine may be expected. In addition, because MDPV can be consumed in a number of different ways and has a short duration of action, it may be more appealing to drug users. With respect to physical dependence and tolerance, there is insufficient evidence on which to base any specific conclusions regarding MDPV at this point in time.



DGO comment - please provide some plain language examples on the assessment of abuse liability and dependence potential. Simply re-word what Tara sent earlier.

To initiate the regulatory process, CSTD is working with Treasury Board Secretariat to complete a triage questionnaire for this regulatory proposal. It is hoped that this will be complete by the end of July 2012.



5. Please add in any other details you think would be useful.

Canadian media reports have originated primarily from Eastern provinces, including New Brunswick and Nova Scotia. On May 18, 2012, health officials in northern Nova Scotia issued a warning concerning the dangers posed by "bath salts", including reports of cases where use has resulted in the user requiring emergency care.

Jocelyn

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada

s.21(1)(a)

s.21(1)(b)

Tel: (613) 946-0125 Fax: (613) 946-4224

Andria Sherstone

Please see comments/requested revisions below...

2012-05-24 02:14:24 PM

From: Andria Sherstone/HC-SC/GC/CA
To: Johanne Beaulieu/HC-SC/GC/CA@HWC
Cc: Jocelyn Kula/HC-SC/GC/CA@HWC, Tara Phillips/HC-SC/GC/CA@HWC, CSTD-OCS-DO
Date: 2012-05-24 02:14 PM
Subject: MDPV - Revisions required

Please see comments/requested revisions below. Please have a revised version to DGO no later than 3:00.

1. A brief explanation of what bath salts are and what their ingredients are.

Over the past several months, there have been increasing media reports on synthetic stimulants sold under the guise of "bath salts" appearing in Canada. Law enforcement and border seizures of products labelled as "bath salts" have also been increasing. Such products are not genuine bath salt products, i.e., epsom salts, intended for softening/cleansing the skin, but contain one or more substances with stimulant properties such as mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and 3,4-methylenedioxypyrovalerone (MDPV). MDPV, in particular, is most often sold as a powder and is reported to be administered through a wide range of modalities, with oral ingestion, injection, and nasal insufflation (snorting) being most prevalent. While the extent of their use in Canada is unknown, "bath salts" are available for purchase on the Internet and may be found in alternative lifestyle stores. Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky". These products may also be labelled as "plant food" and/or "not for human consumption" to circumvent regulatory control.

CAS comment - do all Bath Salts contain all 3 ingredients (MDPV, Mephedrone, Methylone)? Please clarify.

2. How seizure data has indicated that MDPV only bath salts are becoming more prevalent.

From January 2010 to present, Health Canada's Drug Analysis Service (DAS) has identified MDPV or mephedrone in 461 exhibits of suspected controlled substances seized by law enforcement. 444 of these exhibits were found to contain MDPV and 17 were found to contain mephedrone.

CAS comment - what about MDPV alone?

3. HC has acted on the data by initiating work to schedule (break down the work in progress e.g. Triage questionnaire, pharmacology assessment, etc. and associated timelines)

As part of its scheduling assessment, Health Canada let an external contract aimed at assessing the abuse liability and dependence potential of MDPV. The assessment was completed in May 2012, and a comprehensive scheduling assessment is now underway with a target timeline of August 2012.

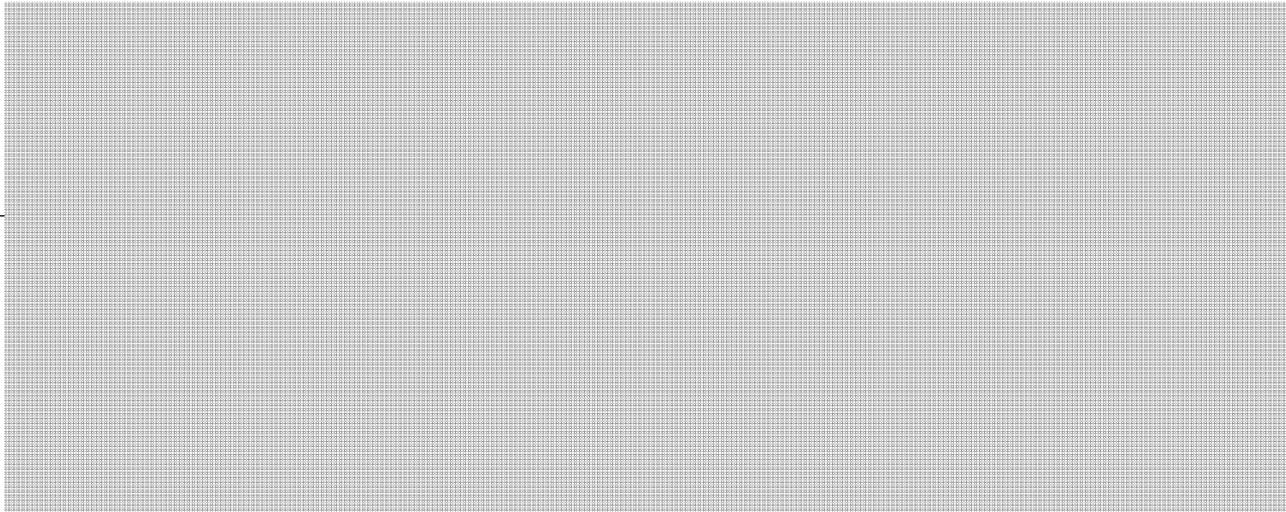
DGO comment - please provide some plain language examples on the assessment of abuse liability and dependence potential. Simply re-word what Tara sent earlier.

To initiate the regulatory process, CSTD is working with Treasury Board Secretariat to complete a triage

s.21(1)(a)

s.21(1)(b)

questionnaire for this regulatory proposal. It is hoped that this will be complete by the end of July 2012.



5. Please add in any other details you think would be useful.

Canadian media reports have originated primarily from Eastern provinces, including New Brunswick and Nova Scotia. On May 18, 2012, health officials in northern Nova Scotia issued a warning concerning the dangers posed by "bath salts", including reports of cases where use has resulted in the user requiring emergency care.

Andria Sherstone
DGO Advisor / Conseillère
Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au
tabagisme
Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada / Santé Canada
Tel: (613) 948-8951

159

Fw: URGENT: MO Request - Bath Salts

Jocelyn Kula to: Tara Phillips

2012-05-24 11:55 AM

Cc: "Johanne Beaulieu", "Andria Sherstone"

History: This message has been replied to.

Hi Tara,

Can you take care of this right away?

Sorry for delay Andria; am in intense planning mtg and have not been looking at bb too much....

Sent by blackberry

Andria Sherstone

----- Original Message -----

From: Andria Sherstone

Sent: 2012-05-24 11:10 AM EDT

To: Johanne Beaulieu

Cc: Jocelyn Kula

Subject: Re: URGENT: MO Request - Bath Salts

Thanks Johanne.

One quick question - would it be possible to include some preliminary results from the assessment of abuse liability and dependence potential (#3)? Just some general comments that could demonstrate that there is some evidence to back up scheduling?

Thanks!

-A

Andria Sherstone

DGO Advisor / Conseillère

Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au tabagisme

Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada / Santé Canada

Tel: (613) 948-8951

Johanne Beaulieu Good Morning Andria! Here you are. 2012-05-24 10:54:08 AM

From: Johanne Beaulieu/HC-SC/GC/CA

To: Andria Sherstone/HC-SC/GC/CA@HWC

Cc: CSTD-DGO, CSTD-OCS-DO, "Jocelyn Kula" <jocelyn.kula@hc-sc.gc.ca>

Date: 2012-05-24 10:54 AM

Subject: Re: URGENT: MO Request - Bath Salts

Good Morning Andria!

Here you are.

Johanne

160



RE: Proposed Scheduling Entry for MDPV 
Guy Aucoin to: Tara Phillips
Cc: Nathan Isotalo, DAS_mgr

2012-05-29 03:59 PM

Bonjour Tara,

Since 3,4-methylenedioxypropylvalerone (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues will all be controlled under CDSA, We don't see the added value to specify the isomer position. For us it could be a nightmare to differentiate the 3,4 isomer and the 2,3 isomer. If 2-3 is included, DAS would suggest that you use similar wording as you have used with the BZP and TFMPP::

Methylenedioxypropylvalerone (MDPV), namely 3,4-methylenedioxypropylvalerone and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues

Benoit Archambault
Gestionnaire Laboratoire/Lab Manager
Service Analyse des Drogues/Drug Analysis Service
Santé Canada/Health Canada
Tel : 450.928.4027
Fax: 450.928.4144
Cel.: 514.973.0823
benoit.archambault@hc-sc.gc.ca
Directeur exécutif, Laboratoires et Services corporatifs -
Executive Director, Laboratories and Corporate Services
Santé Canada , Région du Québec - Health Canada , Quebec Region
Tél / Tel : (450) 928-4100
Télécopieur / Fax : (450) 928-4424

Tara Phillips

Hi Guy, As you know, we are proceeding with work t...

2012-05-28 16:24:11

De : Tara Phillips/HC-SC/GC/CA
A : Guy Aucoin/HC-SC/GC/CA@HWC
Cc : Nathan Isotalo/HC-SC/GC/CA@HWC
Date : 2012-05-28 16:24
Objet : Proposed Scheduling Entry for MDPV

Hi Guy,

As you know, we are proceeding with work to schedule MDPV under the CDSA.

The next step will be the issuance of a *Notice to interested parties* in *Canada Gazette*, Part I, which is planned for June 2012. I have attached the latest draft of this document.

The proposed scheduling entry is:

3,4-methylenedioxypropylvalerone (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues

If you have any comments on the proposed scheduling entry or the Notice, could you please let me know by COB this Friday, June 1st?

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

[pièce jointe "NOI MDPV 2012-05-28.doc" supprimée par Guy Aucoin/HC-SC/GC/CA]

162



Head's Up re Potential Media Coverage on Bath Salts

Jocelyn Kula to: Johanne Beaulieu

2012-05-29 05:30 PM

Cc: Tara Phillips, Nathan Isotalo, Andria Sherstone, Christine Roush, Nicole Prentice, Suzanne Desjardins

Just got off the phone with [REDACTED] Addiction Services for Pictou County in Nova Scotia. [REDACTED] was calling to advise OCS of a recent trend (since the 1st of April) of increasing numbers of persons presenting to the local ER or drug detox unit, further to having used bath salts and experiencing effects such as distress, psychosis, anxiety, racing heart rate, etc. This phenomenon appears to be quite localized to Pictou County and neighbouring Colchester County.

While their local hospital labs do not have the capacity to test for MDPV or mephedrone (only Halifax is equipped and they are unwilling to prioritize assay development and sample testing when they are not seeing the same type of patients presenting), patient accounts and a confirmed RCMP-tested seizure would seem to indicate that the primary substance in question is MDPV. Local law enforcement intelligence seems to suggest that there are likely a couple of small labs bringing the substance into Canada in raw or finished product form and then distributing it through their local network of dealers. Patients, who range in age from 20 to mid-40s, fairly evenly split between male and female, and were all experienced drug users, have indicated that they obtained the drug on the street (not via the Internet or a store) and that they were sometimes told it was like ecstasy or that it was amphetamine. Local law enforcement has also reported hearing that some dealers were mixing MDPV with marijuana and offering it for sale as "space weed".

In response the Pictou Health Services Department has formed a number of sub-committees aimed at collecting and sharing information and collaborating on responsive actions. They have also launched a media awareness campaign, and in response, [REDACTED] advised that the CBC National and the Aboriginal People's Television Network are both going to run segments on bath salts this week. The CBC National piece is apparently supposed to air Wednesday night.

[REDACTED] then asked whether Health Canada was aware of these products and what action, if any, it was taking. I advised [REDACTED] that we were aware of these products, and that the Department was in the process of determining next steps. [REDACTED] asked some questions about the scheduling process, and I asked him whether he would be willing to share the ER incident stats that his county has been collecting as well as the materials they have developed for their media awareness campaign. [REDACTED] agreed and said he would send them to me by email in the next day or so.

Johanne and Andria- the draft NOI for MDPV is now with ORS for comment but should be back in DGO this week. Christine and Tara are working on updated media lines on bath salts.

Jocelyn

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé

163



For Your Review: Revised "MDPV in Bath Salts" QP Note
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-05-30 10:40 AM

Hi Jocelyn,

Please see below, for your review, a revised QP note on bath salts. The April version included mephedrone in the title and the anticipated question. I removed them (can't do redline and strikeout in those sections, it seems) because I think the issue now is really MDPV, given the recent stats from DAS.

The only change to the text below from what you approved last Wednesday, May 23rd (update was following health warning in NS) is to the "Synopsis" section to mention recent coverage today on CBC and to change the statement about the substances in bath salts (it previously said bath salts contained a mix of the three substances, which we now know is not the case, at least in the samples seen by DAS).

Thank you,

Tara

QUESTION PERIOD NOTE NOTE POUR LA PÉRIODE DE QUESTIONS

Date:	May 30, 2012
Classification:	HECS PROTECTED - SESC PROTÉGÉ

English:

MDPV IN BATH SALTS

SYNOPSIS - SOMMAIRE

English:

Health officials in northern Nova Scotia have issued a warning concerning the dangers posed by an emerging street drug known as "bath salts". On May 30, 2012, there was a feature story on the use of "bath salts" on CBC Radio's The Current, adding to the growing body of media reports. "Bath salts" may contain one or more substances with stimulant properties such as MDPV (3,4-methylenedioxypropylone), mephedrone and/or methylone. Such products are likely labelled as "bath salts" in order to appear legal. Both methylone and mephedrone are considered controlled substances in Canada, while MDPV is not yet included in one of the Schedules to the Controlled Drugs and Substances Act (CDSA). Canadian law enforcement and border services are seeing an increasing trend in the incidence of "bath salts" seizures.

ANTICIPATED QUESTION - QUESTION PRÉVUE

English:

What is the Government doing about MDPV in bath salts?

English:

- This Government is very concerned about the public health and safety risks associated with the use of "bath salts". ~~the recent drug analyses and seizures of so-called "bath salts" containing a substance called MDPV.~~
- Health Canada is assessing MDPV, a key ingredient in "bath salts", for scheduling under the *Controlled Drugs and Substances Act*. ~~Health Canada will be working with law enforcement agencies to determine the most appropriate next steps to address the public health and safety risks associated with the use of MDPV.~~
- This Government is committed to controlling substances that produce harm to health and to society when abused.

Français:

BACKGROUND - CONTEXTE

English:

A number of recent media articles in both the United States and Canada have highlighted dangers posed by products labelled and marketed as "bath salts" which are being used as amphetamine-like stimulants. These products are not genuine bath salt products at all, which are typically composed of water soluble mineral salts and are added to water for the purpose of cleansing, softening and/or perfuming the skin.

Canadian media reports have originated primarily from Eastern provinces, including New Brunswick and Nova Scotia. On May 18, 2012, health officials in northern Nova Scotia issued a warning concerning the dangers posed by "bath salts", including reports of cases where use has resulted in the user requiring emergency care.

~~Preliminary reports indicate that~~ The psychoactive ingredients contained in "bath salts" products may include mephedrone, methylone and/or MDPV (3,4-methylenedioxypropylone). In addition, there have been reports of "bath salts" being used to lace other drugs such as marijuana.

Mephedrone and methylone are analogues of amphetamine and is thus considered to be included in Item 1 of Schedule III to the CDSA. ~~Adverse effects associated with the use of amphetamines can include seizures, cerebral hemorrhage, high fever, coma or death.~~

MDPV is a central nervous system stimulant. Adverse physical effects associated with the use of stimulants can include palpitations, irregular or abnormal heartbeat, heart attack or cardiovascular collapse. MDPV use has also been associated with severe panic attacks and anxiety, as well as hallucinations and psychosis. ~~whose use can cause increased blood pressure and increased heart rate. The use of MDPV has also been associated with panic attacks, anxiety and hallucinations, suicidal thoughts, tendencies and death.~~ MDPV is not regulated as a controlled substance in Canada.

~~From other analyses, from January 2010 to present, Health Canada's Drug Analysis Service (DAS) has identified MDPV or mephedrone in 461332 exhibits of suspected controlled substances seized by law enforcement. 444315 of these exhibits were found to contain MDPV alone. Only and 17 were found to contain mephedrone.~~

The CDSA prohibits all activities, e.g., possession, production, distribution, sale, import, and/or export, involving substances listed in one of the Schedules to the Act, unless authorized by regulation. Health Canada considers several factors in determining whether the scheduling of a substance under the Controlled Drugs and Substances Act (CDSA) is warranted. These include:

- Overall risk to public health and safety posed by the substance.
- Chemical and pharmacological similarity to other substances already regulated under the CDSA;
- Legitimate uses of the substance (i.e., therapeutic, industrial or commercial);
- Potential for abuse and risk of addiction associated with the substance;
- Extent of actual abuse of the substance in Canada and internationally; and
- International requirements and trends in international control.

In the United States, the Drug Enforcement Administration has recently used its emergency scheduling authority to temporarily ban mephedrone, MDPV and methyldone. MDPV has also recently been banned in the United Kingdom.

No drug products containing MDPV or mephedrone have been approved for sale in Canada.

~~Health Canada will continue to work with law enforcement agencies in determining the most appropriate next steps in addressing the public health and safety risks associated with the use of MDPV.~~

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

Contact/Personne ressource : Jocelyn Kula/HC-SC/GC/CA	Tel. no./No de tél. 946-0125	Approved by/ Approuvé par Hilary Geller, ADM (HECS/SESC)	Tel. no./No. de tél. 946-6701
	Mobile/ Cellulaire:	Title/ Titre:	Mobile/ Cellulaire:
Alternate/ Secondaire:	Telephone/ Téléphone:		
	Mobile/ Cellulaire:		

164



Fw: As requested

Andria Sherstone to: Johanne Beaulieu, Jocelyn Kula

2012-05-30 11:11 AM

Cc: Tara Phillips, Denis Arsenault, CSTD-OCS-DO, SoniaH Lindblad1

History: This message has been forwarded.

Hi all,

Please see the urgent request from DMO below. This is a follow-up to the one pager we sent up on MDPV last week.

Could you please provide a Q&A as per Ian's e-mail.

DGO will require this by noon. By e-mail is fine.

Thanks!

-A

Andria Sherstone

DGO Advisor / Conseillère

Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au tabagisme

Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et de la sécurité des consommateurs

Health Canada / Santé Canada

Tel: (613) 948-8951

----- Forwarded by Andria Sherstone/HC-SC/GC/CA on 2012-05-30 11:07 AM -----

From: Ian Hobler/HC-SC/GC/CA
To: Andria Sherstone/HC-SC/GC/CA@HWC
Date: 2012-05-30 11:01 AM
Subject: Fw: As requested

Hi Andria.

Could you please ask OCS to provide a Q and A on the difference in authorities for scheduling under the CDSA and the US CSA (including temporary for the US)? ASAP would be great.

Thanks.

Ian

----- Forwarded by Ian Hobler/HC-SC/GC/CA on 2012-05-30 10:59 AM -----

From: Steven Schwendt/HC-SC/GC/CA
To: Ian Hobler/HC-SC/GC/CA@HWC
Cc: Linsey Hollett/HC-SC/GC/CA@HWC
Date: 2012-05-30 10:24 AM
Subject: Re: Fw: As requested

Hi - further to our discussion yesterday, can we get a description or short q/a on the difference in authorities to take interim action in the US and Canada (i.e., how is it that the US can temporarily schedule MDPV as a controlled substance whereas in Canada no action can be taken until the regulatory process

000696

to schedule it under the CDSA is complete?)

Thanks,
Steve

Ian Hobler They are.

2012-05-29 05:58:35 PM

From: Ian Hobler/HC-SC/GC/CA
To: Steven Schwendt/HC-SC/GC/CA@HWC, Linsey Hollett/HC-SC/GC/CA@HWC
Date: 2012-05-29 05:58 PM
Subject: Re: Fw: As requested

They are.

Steven Schwendt thanks x 2 (as I got from Ian as well). Hope th...

2012-05-29 05:57 PM EDT

From: Steven Schwendt
To: Linsey Hollett; Ian Hobler
Cc:
Date: 2012-05-29 05:57 PM EDT
Subject: Re: Fw: As requested

thanks x 2 (as I got from Ian as well). Hope they're the same versions.

Steve

Linsey Hollett Just sent this to George 1 minute ago. Forgot to...

2012-05-29 04:27:49 PM

From: Linsey Hollett/HC-SC/GC/CA
To: Steven Schwendt/HC-SC/GC/CA@HWC
Date: 2012-05-29 04:27 PM
Subject: Fw: As requested

Just sent this to George 1 minute ago. Forgot to copy you.

Apologies.

Linsey Hollett
A/Director / Directrice
Assistant Deputy Minister's Office / Bureau du sous-ministre adjoint
Healthy Environments and Consumer Safety Branch /
Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada / Santé Canada
Phone / Téléphone : 613-946-6705

----- Forwarded by Linsey Hollett/HC-SC/GC/CA on 2012-05-29 04:26 PM -----

From: Linsey Hollett/HC-SC/GC/CA
To: George Kitchen/HC-SC/GC/CA@HWC
Date: 2012-05-29 04:25 PM
Subject: As requested

Information on bath salts as requested on Thursday.

[attachment "Bath Salts Info for MO.doc" deleted by Steven Schwendt/HC-SC/GC/CA]

Linsey Hollett
A/Director / Directrice
Assistant Deputy Minister's Office / Bureau du sous-ministre adjoint
Healthy Environments and Consumer Safety Branch /
Direction générale de la santé environnementale et
de la sécurité des consommateurs
Health Canada / Santé Canada
Phone / Téléphone : 613-946-6705

165



Fw: Q&A on MDPV (U.S. emergency scheduling)
Johanne Beaulieu to: Andria Sherstone, soniah.lindblad1
Cc: Tara Phillips, jocelyn.kula

2012-05-30 12:19 PM

Approved.

Johanne

Johanne Beaulieu

Director | Directrice

Office of Controlled Substances | Bureau des substances contrôlées

Controlled Substances and Tobacco Directorate | Direction des substances contrôlées et de la lutte au tabagisme

Healthy Environments and Consumer Safety Branch | Direction générale de la santé environnementale et de la sécurité des consommateurs

123 Slater Street, Room D-387 | 123 rue Slater, Pièce D-387

Ottawa, Ontario K1A 0K9

(T) 613 952-2177

(F) 613 946-4224

----- Forwarded by Johanne Beaulieu/HC-SC/GC/CA on 2012-05-30 12:18 PM -----

From: Tara Phillips/HC-SC/GC/CA
To: Johanne Beaulieu/HC-SC/GC/CA@HWC
Cc: Jocelyn Kula/HC-SC/GC/CA@HWC, CSTD-OCS-DO
Date: 2012-05-30 11:58 AM
Subject: Q&A on MDPV (U.S. emergency scheduling)

Hi Johanne,

Here is the additional Q&A on MDPV, for your review. Sorry for the delay.

Tara

Q - What is the difference in authorities to take interim scheduling action in the US and Canada (i.e., how is it that the US can temporarily schedule MDPV as a controlled substance whereas in Canada no action can be taken until the regulatory process to schedule it under the CDSA is complete?)?

In 1984, the United States amended its *Controlled Substances Act* to include a provision which allows the Drug Enforcement Administration (DEA) to add a substance, on a temporary basis, to Schedule I when it is necessary to avoid an imminent hazard to public safety. Emergency scheduling takes effect within 30 days and the temporary scheduling of the substance is valid for only one year, after which it expires, unless the substance has been permanently scheduled using the conventional regulatory process. An extension of up to six months may be granted if formal scheduling procedures have been initiated. Recently, a bill was introduced to extend the validity of the temporary scheduling to 2 years and the extension to 1 year. Emergency scheduling was used for the first time for MDMA (ecstasy) in 1988 and has been used for a variety of other substances including three synthetic stimulants sold under the guise of "bath salts" (3,4 methylenedioxyprovalerone (MDPV), mephedrone and methylene) in October 2011.

The *Controlled Drugs and Substances Act* does not contain emergency scheduling authorities. While a number of federal statutes including among others the *Food and Drugs Act*, the

Quarantine Act and the *Canadian Environmental Protection Act* (CEPA) were amended to include interim order powers, further to the passage of the *Public Safety Act*, the CDSA does not contain this power.

Schedules to the *Controlled Drugs and Substances Act* (CDSA) can only be amended by regulation. In the typical federal regulatory process, as governed by the *Statutory Instruments Act*, departments wishing to make or amend a regulation prepare a regulatory proposal that is then submitted to Treasury Board (TB) for consideration for pre-publication in *Canada Gazette*, Part I (CG1). Following a minimum 30-day comment period (75 days for regulations with an impact on international trade), a final proposal is developed and submitted for approval by TB and the Governor in Council. The final regulation is then registered and published in *Canada Gazette*, Part II (CG2).

The entire process from initial analysis through publication in CG2 typically takes an average of 18 to 24 months. While there have been instances in the past when a substance has been scheduled in an accelerated timeline by seeking an exemption from pre-publication in CG1, these have required Health Canada to obtain support from Treasury Board Secretariat. In other words, there is no specific authority in the CDSA that allows the Minister of Health to automatically schedule a substance under an accelerated timeline.

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-30 11:31 AM -----

From: Andria Sherstone/HC-SC/GC/CA
To: Johanne Beaulieu/HC-SC/GC/CA@HWC, Jocelyn Kula/HC-SC/GC/CA@HWC
Cc: Tara Phillips/HC-SC/GC/CA@HWC, Denis Arsenault/HC-SC/GC/CA@HWC, CSTD-OCS-DO, SoniaH Lindblad1/HC-SC/GC/CA@HWC
Date: 2012-05-30 11:11 AM
Subject: Fw: As requested

Hi all,

Please see the urgent request from DMO below. This is a follow-up to the one pager we sent up on MDPV last week.

Could you please provide a Q&A as per Ian's e-mail.

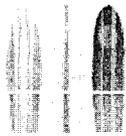
DGO will require this by noon. By e-mail is fine.

Thanks!

-A

Andria Sherstone
DGO Advisor / Conseillère
Controlled Substances and Tobacco Directorate / Direction des substances contrôlées et de la lutte au tabagisme
Healthy Environments and Consumer Safety Branch / Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada / Santé Canada
Tel: (613) 948-8951

166



CBC.ca: 'Bath salts' addict warns of street drug's dangers

HC_Media_SC to:

Sent by: Nicolas Frate

Bcc: Nathan Isotalo

2012-05-30 11:58 AM

Distribution group/Groupe de distribution: Controlled Substances - Substances contrôlées -
HECSB/DGSESC, DComm,

May 30, 2012 11:51 AM ET

'Bath salts' addict warns of street drug's dangers

Source: cbc.ca/health

It's a drug with a harmless-sounding name, but a Nova Scotia man knows the horrors of bath salts first-hand.

Bath salts are not Epsom salts and have nothing to do with the substances that people put in their bath tub.

The drugs used in the concoction are legal in Canada. There is one controlled substance, but producers can get that online or at a pharmacy without a prescription.

Bath salts are comparable to a mix of cocaine and amphetamine. It's a long-lasting street drug that produces extreme euphoria. When that feeling disappears, the user craves more.

Taking them can result in serious consequences, including death.

John's first big trip on bath salts was in February. He was strung out on the drug for eight days with virtually no sleep until he crashed.

He says the feeling was scary even for an experienced drug user.

"Felt like I wanted to kill me or kill somebody else. Horrible feeling of sketchiness, constantly looking over your shoulder or peeking out around your curtains or windows, hiding under the blankets."

John is not his real name. He says he decided to talk to CBC because he felt he should warn people about the dangers of bath salts.

John, who is in his mid-40s, got the drugs from a friend. He doesn't remember how many times he smoked them during that eight-day stretch.

He was told he looked like a corpse.

"A person actually walked into the room and told me that he thought I was almost dead."

John spent a day and a half in hospital after that.

"I come out of the hospital; I went home and never moved outside my house for another week."

Weeks later, John went to the detox unit in Pictou County, where he experienced the same paranoia.

Many dangers

Doctors in northern Nova Scotia say they are seeing two to three people on bath salts a week. They warn of the dangers, including heart attacks, kidney failure, extreme aggression and death.

"You basically take cocaine and multiply it by a factor of 10 and you have this," said Dr. Heidi-Marie

Farinholt, a physician at Aberdeen Hospital in New Glasgow.

Farinholt says when it comes to violence and drugs, bath salts are among the worst. She did her training in Baltimore, where she saw a lot of cases involving drugs and guns.

"I have to say this drug scares me more than any of that ever did," she told CBC last week.

Bath salts are banned in the United States, Australia, the United Kingdom and many other European countries. ~~Canada is still considering what to do.~~

In an email to CBC, Health Canada said it does not recommend the use of bath salts because of their potentially dangerous health effects and also because little is known about their potential long-term effects on the brain and body.

<http://www.cbc.ca/news/health/story/2012/05/30/ns-bath-salts-user.html?cmp=rss>

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167



Fw: Proposed Scheduling Entry for MDPV
Nathan Isotalo to: Tara Phillips

2012-05-30 01:20 PM

Hi Tara

As discussed, since we need to include the 2,3- MDPV we can use the wording of the BZP as suggested by DAS. Nathan.

----- Forwarded by Nathan Isotalo/HC-SC/GC/CA on 2012-05-30 01:18 PM -----

From: Nathan Isotalo/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Date: 2012-05-30 11:02 AM
Subject: Re: Fw: Proposed Scheduling Entry for MDPV

Hi Tara,

The issue of analytical detection and resolution is always an issue when the methodologies /standards have not yet fully been developed or elucidated.

The fact is MDPV has isomers and the 2,3-MDPV is also a potential designer drug and thus, needs to be controlled. How do you feel the public or media would react if we schedule only one and not all?

For this reason, we can not impose controls on just the 3,4-MDPV and need to include the term isomers.

Nathan.

Tara Phillips

Hi Nathan, Please let me know by COB if you h...

2012-05-30 10:50:38 AM

From: Tara Phillips/HC-SC/GC/CA
To: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-05-30 10:50 AM
Subject: Fw: Proposed Scheduling Entry for MDPV

Hi Nathan,

Please let me know by COB if you have any comments on DAS' proposal below.

Thank you,

Tara

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-30 10:50 AM -----

From: Guy Aucoin/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Cc: Nathan Isotalo/HC-SC/GC/CA@HWC, DAS_mgr
Date: 2012-05-29 03:59 PM
Subject: RE: Proposed Scheduling Entry for MDPV

Bonjour Tara,

Since 3,4-methylenedioxypropylvalerone (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues will all be controlled under CDSA, We don't see the added value to specify the isomer position. For us it could be a nightmare to differentiate the 3,4 isomer and the

2,3 isomer. If 2-3 is included, DAS would suggest that you use similar wording as you have used with the BZP and TFMPP::

Methylenedioxypropylone (MDPV), namely 3,4-methylenedioxypropylone and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues

Benoit Archambault
Gestionnaire Laboratoire/Lab Manager
Service Analyse des Drogues/Drug Analysis Service
Santé Canada/Health Canada
Tel : 450.928.4027
Fax: 450.928.4144
Cel.: 514.973.0823
benoit.archambault@hc-sc.gc.ca
Guy Aucoin
Directeur exécutif, Laboratoires et Services corporatifs -
Executive Director, Laboratories and Corporate Services
Santé Canada , Région du Québec - Health Canada , Quebec Region
Tél / Tel : (450) 928-4100
Télécopieur / Fax : (450) 928-4424

Tara Phillips

Hi Guy, As you know, we are proceeding with work t...

2012-05-28 16:24:11

170



For Docket
Tara Phillips to: Ian McGillivray
Cc: Nathan Isotalo

2012-05-30 03:27 PM

Hi Ian,

As discussed, here are two attachments for a docket to be routed up for Cathy Sabiston's approval.

Thank you,

Tara



NOI MDPV 2012-05-30 FR.doc



NOI MDPV 2012-05-30.doc

175



For Your Review: Accelerated Critical Path for MDPV Scheduling

Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-05-30 08:17 PM

Hi Jocelyn,

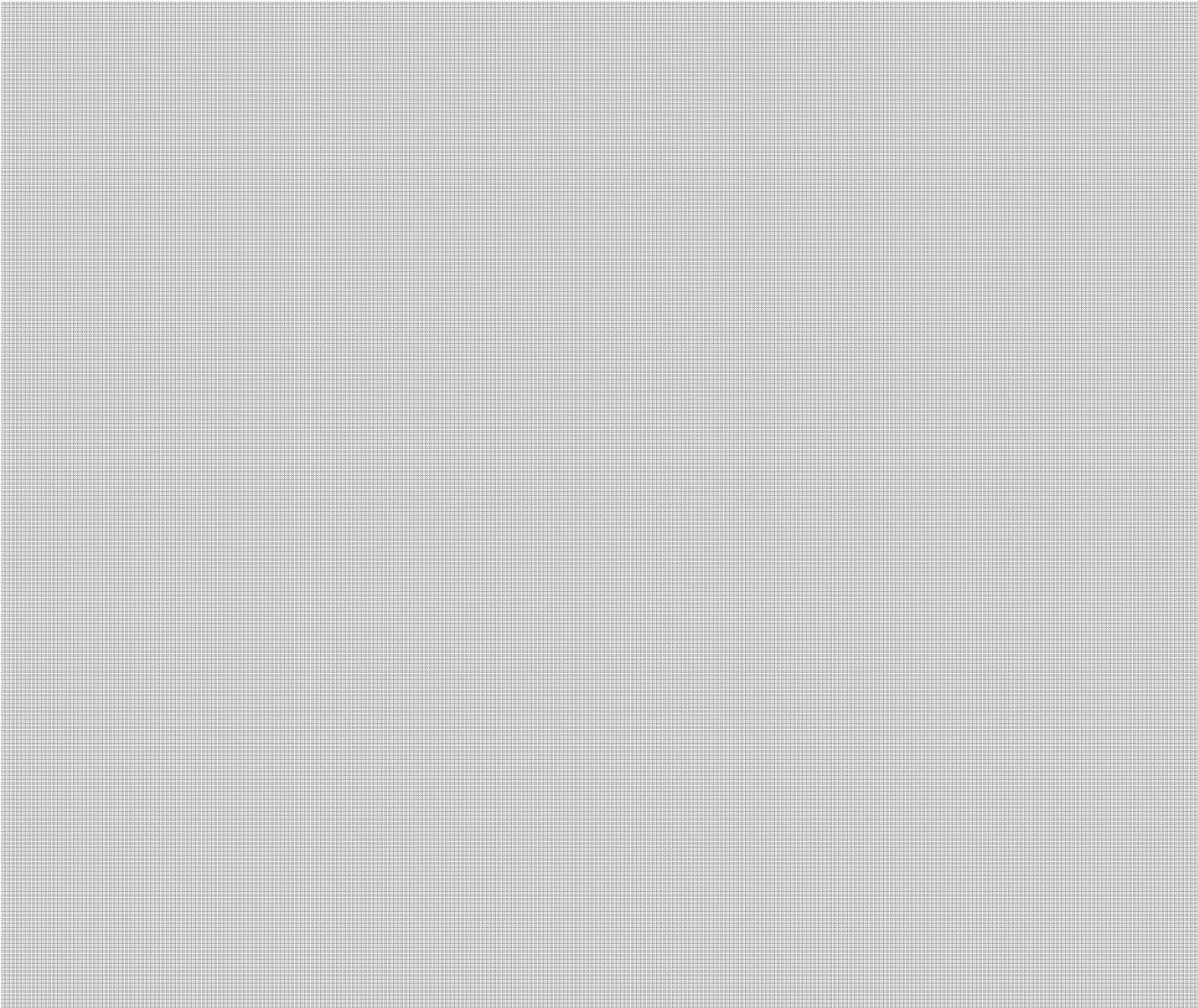
Further to Cathy's request for a 'critical path' for the scheduling of MDPV, please see draft email below. I have included information from a telephone conversation I had late today with Kyle Burns, TBS.

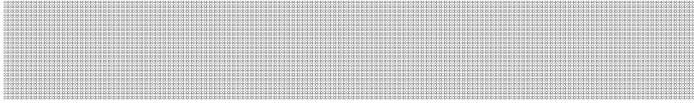
Thank you,

Tara
946-6521

Cathy,

The following represents the critical path that could be followed in order to schedule MDPV as quickly as possible, informed by consultation with Treasury Board Secretariat:





<insert signature>

s.21(1)(a)
s.21(1)(b)

179



Re: Adverse Reactions (MDPV in Bath Salts) 
Lucie Olson to: Tara Phillips
Cc: Nathan Isotalo, Karen Fortin, Heather Morrison, Mimi Hum

2012-05-31 08:44 AM

Hi Tara,

I'll forward you our response to the media enquiry, which is the same question as the one you listed below. The Canada Vigilance Program would not have any adverse reaction reports for this type of substance as it is not authorised health products. Our search of the database for the term "Bath Salts" returned no report and we just checked for "methylenedioxypropylone" and "MDPV" and there is nothing either (see details below). If any report came to the Canada Vigilance Program, we would re-direct it to HECS since it's outside of our scope.

This is to confirm that, for the period covering January 1, 1965 to February 29, 2012, Health Canada received no adverse reaction (AR) reports involving the suspect products "methylenedioxypropylone" or "MDPV".

Caveat: Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Search results on behalf of the Canada Vigilance Program:

In response to your request dated May 30, 2012, a search of the Canada Vigilance Program Database was performed.

The parameters of the search were as follows:

1. reports received for **methylenedioxypropylone** or **MDPV** with a suspected role;
2. all reported adverse reactions
3. reports received and entered into the database from **January 1, 1965 to February 29, 2012**

Hope this helps,

Lucie Olson
Manager
Adverse Reaction Information Section
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch, Health Canada
Tel: (613) 952-2592
e:mail: lucie_olson@hc-sc.gc.ca

Tara Phillips

Hi Lucie, Thank you very much for your voicema...

2012-05-30 08:58:24 PM

From: Tara Phillips/HC-SC/GC/CA
To: Lucie Olson/HC-SC/GC/CA@HWC
Cc: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-05-30 08:58 PM
Subject: Adverse Reactions (MDPV in Bath Salts)

000708

Hi Lucie,

Thank you very much for your voicemail regarding reports of adverse reactions related to bath salts under the Canada Vigilance Program.

You mentioned a media inquiry in your voicemail and it was likely the same one we were responding to here. Essentially, the question was whether there have been any overdose cases or adverse reactions reports related to bath salts. The particular substance of greatest interest is methylenedioxypropylone (MDPV).

If you have any information to share with us, we would appreciate it, as we are actively working to schedule this substance under the *Controlled Drugs and Substances Act*.

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

180



Fw: MDPV
Tara Phillips to: Jocelyn Kula, Norma Won
Cc: Nathan Isotalo

2012-05-31 09:57 AM

Hi Jocelyn and Norma,

Please see below HPFB's classification of MDPV as a drug from April 2010.

Thank you,

Tara

----- Forwarded by Tara Phillips/HC-SC/GC/CA on 2012-05-31 09:57 AM -----

From: YVES FORTIN/HC-SC/GC/CA
To: Tara Phillips/HC-SC/GC/CA@HWC
Cc: Thea Mueller/HC-SC/GC/CA@HWC
Date: 2012-05-31 09:12 AM
Subject: MDPV

Hi Tara,

As discussed, please find attached our classification of MDPV with respect to the Food and Drugs Act:



- Chem-29 (3,4-methylenedioxypropylvalerone) Classif.wpd

Regards,

Yves

Yves Fortin
Therapeutic Products Classification Committee Secretariat
Office of Science
Bureau of Policy, Science and International Programs
Therapeutic Product Directorate
Health Products and Food Branch
Health Canada
tel. 613-946-4276



Gouvernement du Canada

181

MEMORANDUM

NOTE DE SERVICE

TO
A

Lawrence Cheung
Compliance Officer
Border Integrity Unit
HPFB Inspectorate

SECURITY -- CLASSIFICATION -- DE SÉCURITÉ

OUR FILE -- N/RÉFÉRENCE

YOUR FILE -- V/RÉFÉRENCE

DATE:

April 27, 2010

FROM
DE

Brigitte Zirger
Director, Bureau of Policy, Science and International
Program
TPD

SUBJECT
OBJET :

Classification of Chem-29 (3,4-methylenedioxypropylamphetamine)

Background

On April 22, 2010, HPFB Inspectorate's Border Integrity Unit (BIU) requested advice from TPD's Office of Risk Management on whether Chem-29 (3,4-methylenedioxypropylamphetamine) is an unapproved drug. A shipment of Chem-29 (3,4-methylenedioxypropylamphetamine), also known as MDPV or MDPK, is being held at the border for determination of admissibility by the Inspectorate. The product was being imported into Canada as a white powder in a bag. At issue is the applicability of the *Food and Drugs Act* (F&DA) to MDPV. Should the product be considered to be a drug, it then falls under the purview of the F&DA and the shipment could be stopped from distribution in Canada.

No product containing MDPV has been approved as a human or veterinary drug. This substance is not scheduled under the *Controlled Drugs and Substances Act* (CDSA). It is a psychoactive drug with stimulant properties but has no approved medical use. There are currently no known studies on the effects of MDPV on humans or on proper dosage. It is commonly described as boosting libido and its acute effects may include rapid heartbeat, increase blood pressure, vasoconstriction, sweating, increases alertness & awareness, increased wakefulness and arousal, agitation, and perception of a diminished requirement for food and sleep. At higher doses, MDPV is associated with extreme anxiety.

MDPV was first synthesized as part of a class of stimulants in 1969. It has a chemical structure close to that of propylamphetamine of which it is an analogue with a 3,4-methylenedioxy ring instead of a 4'-methyl group. Schedule IV of the CDSA

-3-

includes "pyrovalerone (4'-methyl-2-(1-pyrrolidinyl)valerophenone) and any salt thereof." Pyrovalerone has been used in certain countries as a psychoactive drug for the clinical treatment of chronic fatigue or as an appetite suppressant.

Considerations:

- MDPV's pharmacological action resembles that of pyrovalerone which has been used in other countries for the clinical treatment of chronic fatigue or as an appetite suppressant
- the product is in the dosage form of a drug (white powder in a bag)
- this product has no known use other than as a stimulant or as an aphrodisiac
- MDPV has an illegal status in Denmark and Sweden

Conclusion:

The shipment of 3,4-methylenedioxyvalerone in question is in the dosage form of a drug and meets the *Food and Drugs Act's* definition of a drug as a substance or a mixture of substances manufactured, sold or represented used in modifying organic functions in humans.

References:

- Joshua C. Yohannan & Joseph S. Bozenko, Jr., (2010, March). U.S. Department of Justice, Drug Enforcement Administration, Special Testing and Research Laboratory, *The Characterization of 3,4-Methylenedioxyvalerone (MDPV)*, Microgram Journal, Volume 7, Number 1
- <http://en.wikipedia.org/wiki/Methylenedioxyvalerone> (Cited 2010 04 22)

121

Emergency Department Visits After Use of a Drug Sold as "Bath Salts" — Michigan, November 13, 2010–March 31, 2011

On May 18, this report was posted as an MMWR Early Release on the MMWR website (<http://www.cdc.gov/mmwr>).

On February 1, 2011, in response to multiple news reports, the Michigan Department of Community Health (MDCH) contacted the Children's Hospital of Michigan Poison Control Center (PCC) regarding any reports of illness in the state caused by the use of recreational designer drugs sold as "bath salts." Unlike traditional cosmetic bath salts, which are packaged and sold for adding to bath water for soaking and cleaning, the drugs sold as "bath salts" have no legitimate use for bathing and are intended for substance abuse. These products can contain stimulant compounds such as 3,4-methylenedioxypropylamphetamine (MDPV) or 4-methylmethcathinone (mephedrone). The PCC told MDCH that, earlier in the day, the PCC had learned that numerous persons had visited the local emergency department (ED) in Marquette County with cardiovascular and neurologic signs of acute intoxication. This report summarizes the subsequent investigation, which identified 35 persons who had ingested, inhaled, or injected "bath salts" and visited a Michigan ED during November 13, 2010–March 31, 2011. Among the 35 patients, the most common signs and symptoms of toxicity were agitation (23 patients [66%]), tachycardia (22 [63%]), and delusions/hallucinations (14 [40%]). Seventeen patients were hospitalized, and one was dead upon arrival at the ED. The coordinated efforts of public health agencies, health-care providers, poison control centers, and law enforcement agencies enabled rapid identification of this emerging health problem. Mitigation of the problem required the execution of an emergency public health order to remove the toxic "bath salts" from the marketplace. Lessons from the Michigan experience could have relevance to other areas of the United States experiencing similar problems.

n=35

From November 2010 to January 2011, the Marquette County ED treated seven patients who arrived at the ED with hypertension, tachycardia, tremors, motor automatisms, mydriasis, delusions, and paranoia. Some patients were violent, placing increased demand on ED staff members. Responding to the cluster also placed additional demands on local law enforcement and foster care, because many patients had young children who needed care while their parents were incapacitated. The patients reported using "bath salts" purchased at a local store for about \$20 a package and labeled "not intended for human consumption." By February 3, a total of 13 cases in Marquette County and one death had been reported to the PCC. Efforts by the local ED, law enforcement, and prosecuting attorney's office led to the execution of an emergency

=7

=13
death

public health order on February 4 by the Marquette County Health Department. The proprietor of the store was ordered to immediately remove from sale and turn over to government authorities any and all products known as White Rush, Cloud Nine, Ivory Wave, Ocean Snow, Charge Plus, White Lightning, Scarface, Hurricane Charlie, Red Dove, White Dove, and Sextasy. The Michigan Department of State Police laboratory tested the White Rush seized from the store and detected the presence of MDPV.

Concurrently, the PCC became aware of two cases elsewhere in the state. On February 5, MDCH used its chemical poisoning regulations to mandate statewide reporting by hospitals of cases of possible "bath salts" intoxication so that cases could be identified and characterized. Health-care providers were notified via the Michigan Health Alert Network about new cases and the potential for severe physical and psychological effects of "bath salts" abuse, and were provided a standardized reporting form. The PCC was designated as an agent of the state so it could receive case reports directly, allowing for mandatory reporting 24 hours a day, 7 days a week. As part of the investigation, patient information for Marquette County cases occurring before mandatory reporting was abstracted from medical charts by a MDCH staff member. A case was defined in a person who visited a Michigan ED during November 13, 2010–March 31, 2011, after self-reported or suspected use of "bath salts" (traditional cosmetic bath salts were excluded), with cardiovascular, neurologic, or psychological signs or symptoms consistent with acute intoxication.

n2

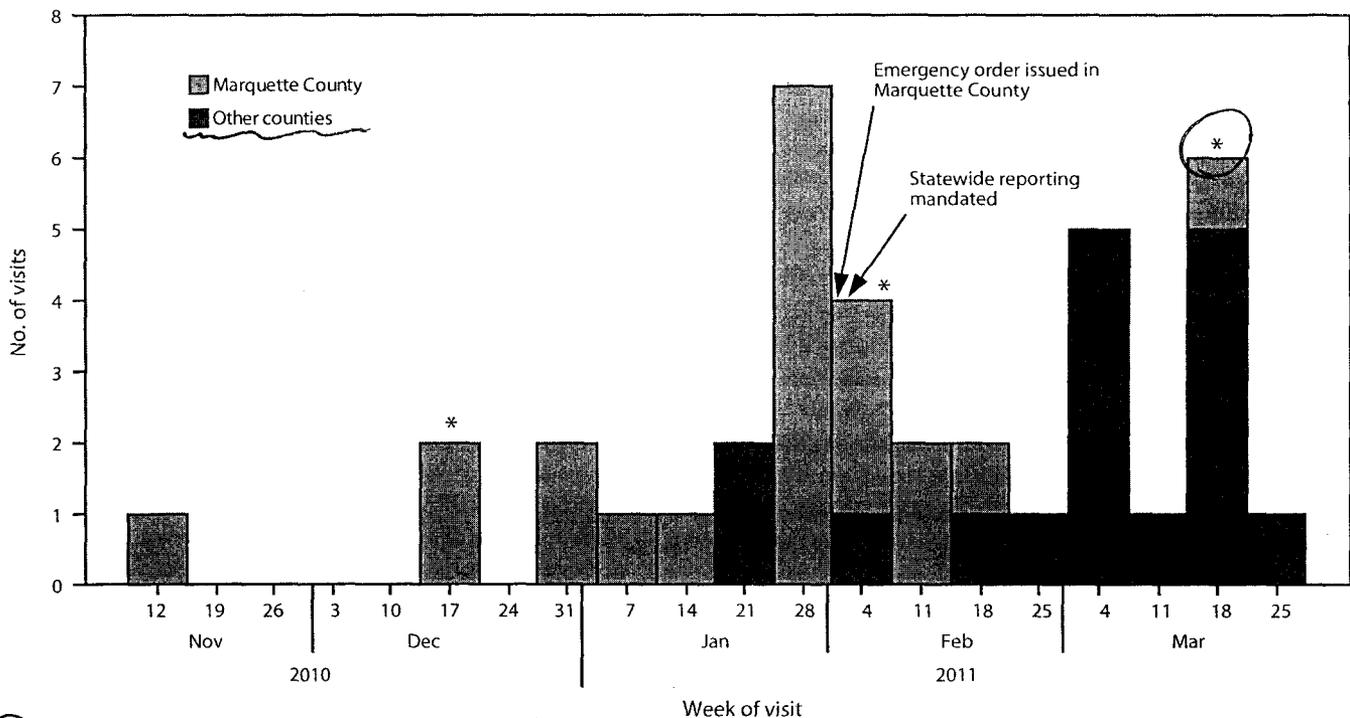
defn

Overall, the investigation identified 35 patients in Michigan, including three who visited the ED twice for "bath salt" abuse (Figure). The patients were aged 20–55 years (median: 28 years) (Table). Nineteen (54%) were men, and 16 (46%) were women. Twenty-four persons (69%) had a self-reported history of drug abuse, with 11 (31%) reporting polysubstance abuse and 12 (34%) intravenous drug abuse. Sixteen persons (46%) had a history of mental illness (e.g., bipolar disorder, schizophrenia, or depression) in their medical records, and six had suicidal thoughts or suspected attempts that might have been related to "bath salts" abuse. Twenty-seven cases (77%) occurred in Michigan's Upper Peninsula region, with 18 cases (51%) occurring in Marquette County. Ten (12%) of Michigan's 83 counties reported cases.

Clinical findings were consistent with intoxication with stimulants. Of the 35 patients, 32 (91%) had neurologic, 27 (77%) had cardiovascular, and 17 (49%) had psychological symptoms. Seventeen patients were hospitalized, 15 were

Morbidity and Mortality Weekly Report

FIGURE. Number of patient visits to emergency departments (N = 38) after exposure to drugs sold as "bath salts," by county and week of visit — Michigan, November 13, 2010–March 31, 2011



* Second emergency department visit by patient.

n.s exp. route unknown
 treated and released from the ED, two left the ED against medical advice, and one was dead on arrival at the ED. Twenty-two of the patients (63%) had injected the drug, nine (26%) had snorted it, and four (11%) had ingested it. For five patients (14%), including the patient who died, the exposure route was unknown, and five patients had more than one exposure route (Table). No relationship was found between the exposure route and severity of illness. Of the 17 patients with known drug test results, 16 (94%) tested positive for other drugs (e.g., marijuana, opiates, benzodiazepines, cocaine, or amphetamines). Toxicology results for the person who died revealed a high level of MDPV, along with marijuana and prescription drugs. Autopsy results revealed MDPV toxicity to be the primary factor contributing to death. The manner of death was ruled accidental, consistent with an attempt to get high.

Of the 17 hospitalized persons, nine were admitted to the intensive care unit (ICU), five were admitted to a general floor, and three were admitted directly to a psychiatric unit. Four persons who were first hospitalized in the ICU or a general floor later were transferred to a psychiatric unit. Treatment generally included a benzodiazepine such as lorazepam to control signs of toxicity; low or moderate doses usually were sufficient. Antipsychotics were used as secondary agents when benzodiazepine sedation was ineffective.

Of three patients who revisited the ED, one had rhabdomyolysis, chest pain, and dizziness but left against medical advice. Two months later, the patient was admitted to the ICU, moved to a psychiatric floor for 12 days, and then transferred to a different hospital for liver failure. The second patient was admitted to the hospital, discharged, and revisited the ED the same day of discharge after again using "bath salts." The third patient was treated in the ED twice, with the visits 1 month apart.

The investigation by MDCH and the PCC is continuing. As of May 16, 2011, a total of 71 emergency department visits by 65 patients who had used "bath salts" had been reported in Michigan since November 13, 2010.

Reported by

Fred Benzie, MPH, MPA, Marquette County Health Dept; Kimberly Hekman, MPH, CDC/CSTE Applied Epidemiology Fellow, Lorraine Cameron, PhD, David R. Wade, PhD, Corinne Miller, PhD, Michigan Dept of Community Health; Susan Smolinske, PharmD, Brandon Warrick, MD, Children's Hospital of Michigan Poison Control Center. Corresponding contributor: Kimberly Hekman, Michigan Dept of Community Health, hekmank@michigan.gov, 517-373-2682.

Morbidity and Mortality Weekly Report

TABLE. Demographic and clinical characteristics for 35 patients evaluated in emergency departments (EDs) after exposure to drugs sold as "bath salts" — Michigan, November 13, 2010–March 31, 2011

Characteristic	No.	(%)
Sex		
Women	16	(46)
Men	19	(54)
Age group (yrs)		
20–29	22	(63)
30–39	5	(14)
40–49	6	(17)
≥50	2	(6)
Exposure route*		
Injected	22	(63)
Snorted	9	(26)
Ingested	4	(11)
Unknown	5	(14)
Additional drug use†		
Marijuana	10	(29)
Opiates	8	(23)
Benzodiazepines	5	(14)
Cocaine	4	(11)
Amphetamines	2	(6)
Signs and symptoms		
Agitation	23	(66)
Tachycardia	22	(63)
Delusions/hallucinations	14	(40)
Seizure/tremor	10	(29)
Hypertension	8	(23)
Drowsiness	8	(23)
Paranoia	7	(20)
Mydriasis	7	(20)
Disposition‡		
Treated in ED and released	15	(43)
Admitted	17	(49)
Dead upon arrival	1	(3)
Left against medical advice	2	(6)

* Five patients reported two exposure routes.

† Seventeen patients had known drug test results.

‡ Most severe disposition was chosen for three patients who revisited the ED.

Editorial Note

Through March 22, 2011, poison control centers representing 45 states and the District of Columbia had reported receiving telephone calls related to "bath salts" in 2011 (1). By April 6, centers had already received five times more "bath salts" calls in 2011 than in 2010 (2). Although "bath salt" abuse has been documented nationwide, this report is the first to summarize the epidemiology of a number of ED cases. Of note in this investigation, nearly half the patients had a history of serious mental illness (e.g., bipolar disorder, schizophrenia, or depression) in their medical records, and 16 of 17 patients with known drug test results tested positive for drugs other than those in the "bath salts."

Drug overdose, including from designer drugs, continues to grow as a public health concern. Multistate investigations have been conducted as a result of exposure to nonpharmaceutical fentanyl (3), levamisole-contaminated cocaine (4), and opiates

What is already known on this topic?

Designer drugs sold as "bath salts" are available at "head shops," convenience stores, gas stations, and on the Internet for recreational drug use.

What is added by this report?

This report is the first public health investigation of emergency department (ED) cases resulting from the use of "bath salts." A total of 35 patients were identified at Michigan EDs during November 13, 2010–March 31, 2011; 17 patients were hospitalized, and one died.

What are the implications for public health practice?

Coordination between public health departments, poison control centers, health-care providers, and law enforcement is important for timely detection that will prevent further drug-related morbidity and mortality.

(5,6). Classes of designer drugs like "bath salts" are intended to have pharmacologic effects similar to controlled substances but to be chemically distinct from them, thus avoiding legal control. "Bath salts" for recreational use are sold at "head shops" and on the Internet with names such as Zoom and White Rush. These products also have been labeled as "plant food" and "pond water cleaner" and sold in ways to circumvent detection or enforcement. Some products are labeled as "novelty collector's items," despite additional, pharmaceutical-like labels that indicate dosage. Before "bath salts," synthetic marijuana (e.g., K2 or Spice) was sold legally in convenience stores and gas stations as "incense."

Designer drugs present an enforcement dilemma. Although MDPV and other chemical constituents of "bath salts" are not listed on state and federal controlled substances schedules, they could be included because of their structural similarity to scheduled chemicals under the analogue provisions of those laws. However, inclusion is problematic because the structure of MDPV is similar to that of medications used to treat conditions such as depression and anaphylaxis. Furthermore, laws also require that scheduled substances be intended for consumption. "Bath salts" typically are labeled "not for human consumption," and thus fail to meet all attributes of a scheduled substance. Therefore, Michigan and other states have pursued legislation to add these chemicals to the state's Schedule I list of controlled substances.

Michigan's investigation involved collaborators from public health, law enforcement, and health care. An emergency order issued by the Marquette County Health Department was effective at stemming "bath salts" abuse locally, and statewide mandated reporting helped detect cases in other counties. These methods might be useful to other jurisdictions where emergent problems need to be addressed quickly. Poison control centers and emergency departments can act as sentinels

Morbidity and Mortality Weekly Report

for discovering new drugs of abuse. Drug treatment programs also might be effective as warning networks. The PCC was designated as an agent of the state to receive mandated reports supporting joint reporting and provision of medical toxicologic consultation. Planning among collaborating agencies is critical to implementing appropriate strategies to reduce drug-related morbidity and mortality.

Acknowledgments

The findings in this report are based, in part, on contributions by S Schreiber, MPH, Michigan Dept of Community Health; S Emerson, MD, L Wallace, Marquette General Health System, K Piggott, MD, Marquette General Health System and Marquette County Health Dept; Michigan Dept of State Police Forensic Science Div; and Michigan Dept of Community Health Bureau of Substance Abuse and Addiction Svcs.

References

1. American Association of Poison Control Centers. U.S. poison centers raise alarm about toxic substance marketed as bath salts; states begin taking action. Alexandria, VA: American Association of Poison Control Centers; March 22, 2011. Available at <http://www.aapcc.org/dnn/portals/0/prrel/bathsaltsmarch22.pdf>. Accessed May 17, 2011.
2. American Association of Poison Control Centers. U.S. poison centers raise alarm about toxic substance marketed as bath salts; states begin taking action. Alexandria, VA: American Association of Poison Control Centers; April 6, 2011. Available at <http://www.aapcc.org/dnn/portals/0/prrel/april6bathsalts.pdf>. Accessed May 17, 2011.
3. CDC. Nonpharmaceutical fentanyl-related deaths—multiple states, April 2005–March 2007. *MMWR* 2008;57:793–6.
4. CDC. Agranulocytosis associated with cocaine use—four states, March 2008–November 2009. *MMWR* 2009;58:1381–5.
5. Paulozzi LJ. Opioid analgesic involvement in drug abuse deaths in American metropolitan areas. *Am J Public Health* 2006;96:1755–7.
6. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. *Addiction* 2009;104:1541–8.

185



For your review: Email to Johanne on MDPV (Sch III vs Sch I)
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-05-31 10:29 AM

Hi Jocelyn,

Please see below, for your consideration, an email to Johanne regarding the issue of Schedule III vs Schedule I for the MDPV Notice.

Thank you,

Tara

Johanne,

In finalizing the *Notice to interested parties* for MDPV, we have been discussing the most appropriate Schedule under the CDSA. If we were to strictly follow past practices, we would propose Schedule IV since MDPV is most similar to pyrovalerone, which is a Schedule IV substance. However, simple possession is not prohibited for Schedule IV substances and given the apparent dangers associated with MDPV, we felt that Schedule III, with its prohibition on simple possession, would be more appropriate. Given the extensive media coverage and statements from health officials about MDPV's effects being severe and the comparisons to cocaine and amphetamine, we are wondering whether it would be best to propose Schedule I. In particular, the comparison to amphetamine is of interest because once the drug portion of the *Safe Streets and Communities Act* is implemented, amphetamine will be moved from Schedule III to Schedule I.

Please advise.

<insert signature>

188



Re: Follow-up to our conversation this morning 
Collin Pinto to: Tara Phillips
Cc: Nathan Isotalo, Karin Suppelsa, Ian Grimwood, Melissa Beauchamp

2012-05-31 11:45 AM

Hi Tara

We will stand down for now then. Let us know if we can be of further assistance.

Best
Collin Pinto

Health Products and Food Branch Inspectorate
Room 359, 250 Lanark Ave. Ottawa, Ontario K1A 0K9
Tel: 613-948-6811
Fax: 613-960-7123

Tara Phillips

Hi Collin, Subsequent to our conversation this m...

2012-05-31 11:02:09 AM

From: Tara Phillips/HC-SC/GC/CA
To: Collin Pinto/HC-SC/GC/CA@HWC
Cc: Nathan Isotalo/HC-SC/GC/CA@HWC
Date: 2012-05-31 11:02 AM
Subject: Follow-up to our conversation this morning

Hi Collin,

Subsequent to our conversation this morning, I have spoken to Yves Fortin of TPD. He provided me with a couple of MECS numbers as examples of messages that were sent out on the status of MDPV.

I think that for now the information from Yves will suffice so please don't consider it necessary to reach out to your organization for additional documentation at this time.

Thanks very much for your help,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

189



Placement of MDPV in Schedules to the CDSA

Jocelyn Kula to: Johanne Beaulieu
Cc: Tara Phillips, Nathan Isotalo, Mélanie Séguin

2012-05-31 11:51 AM

History: This message has been forwarded.

Hi Johanne,

So an interesting issue has come up in progressing our analysis of MDPV and that is into what Schedule we actually want to propose placing it in the forthcoming NOI.

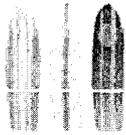
-if we follow past practice of using structural similarity as the main consideration, MDPV should really go into Schedule IV as that is where pyrovalerone is listed
-however, we know that simple possession is not prohibited for Schedule IV substances and given the apparent dangers associated with the use and abuse of MDPV, it would seem that Schedule III is more appropriate and so currently, this is what the NOI suggests
-given the extensive references to cocaine and amphetamine-like effects in the media and in statements from health officials however, another option would be to propose that MDPV be added to Schedule I on the grounds that the offences involving it are worthy of more serious penalties akin to those associated with Schedule I; while I am not suggesting that MDPV is an amphetamine, the comparison is interesting because once the drug portion of the *Safe Streets and Communities Act* (Bill C-10) is implemented, all of the amphetamines in Item 1 of Schedule III will be moved to Schedule I

Do you have any particular views on this? While we can always change our plans after the NOI, it would be my preference to have the NOI state where we intend to put MDPV on a permanent basis.

Happy to discuss
Jocelyn

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224

196



Toronto Star: 'Bath salts' designer drug prompts emergency ban in US

HC_Media_SC to:

2012-05-31 01:28 PM

Sent by: Nicolas Frate

Bcc: Nathan Isotalo

Distribution group/Groupe de distribution: Controlled Substances - Substances contrôlées -
HECSB/DGSESC, DComm,

May 31, 2012 (1:20 PM ET)

'Bath salts' designer drug prompts emergency ban in US

Source: thestar.com, by Lesley Ciarula Taylor

The Toronto ad in Kijiji from last week is gone, but other websites still trade openly and coyly in "bath salts," the designer drug still legal in Canada that's believed to be behind a ghoulish cannibal attack in Miami.

"This bath salt is suitable for making your bathing experience awesome," reads one online selling site. "Take your bathing experience to the next level of euphoria and energy."

That next level, health authorities say, is ugly.

"If you take the very worst of some of the other drugs — LSD and Ecstasy with their hallucinogenic-delusional type properties, PCP with extreme agitation, superhuman strength and combativeness, as well as the stimulant properties of cocaine and meth — and put them all together, this is what you get," said Mark Ryan, director of the Louisiana Poison Centre.

"The psychosis is impressive."

Soaring numbers of severely ill people calling poison-control centres pushed the U.S. Drug Enforcement Agency in October to impose an emergency one-year ban on the three main components of the designer drug — the synthetic stimulants mephedrone, MDPV and methylene.

There were more than 6,000 calls to poison-control centres in the U.S. in 2011, more than 10 times the 2010 number, an American Society of Physics newsletter reported.

Health Canada is examining such a ban, said spokesman Gary Holub.

Mephedrone and methylene are analogues of amphetamine and are already illegal in Canada, he said.

"Health Canada is working with law-enforcement agencies to determine the most appropriate next steps to address the public-health and safety risks associated with the use of MDPV."

The drug, which is difficult to test for and trace, has been creeping into Canada for the past year or more.

"We're aware that it's here," said Dr. Margaret Thompson, medical director of the Ontario Poison Centre.

Underground drug laboratories shift their recipes to sidestep chemical bans, she said.

Tracing it also becomes difficult because so few medical laboratories are set up to detect it in urine.

"Bath salts are not a single substance. They are a compound of concentrated chemicals."

Doctors at Aberdeen Hospital in Nova Scotia have seen a dozen cases in recent weeks, Greg Purvis of Addiction Services at the Pictou Health Authority, told the Halifax Chronicle Herald last week.

"Addiction sets in after only the second or third use of the drug. That's incredibly quick," he said.

"People taking it can become very violent," said Robin Taylor, a medical officer of health in northern Nova Scotia.

"It's very difficult to manage this type of behaviour in the emergency department."

"Bath salts" are sold in packages and jars that resemble commercial tub-soak products – using names such as Ivory Wave, Vanilla Sky, Tranquility and Blue Magic – or as incense or plant food

One online seller advises: "Use sparingly. One application of our bath salts will last for several hours. Please wait several hours between applications to ensure an optimal bathing experience."

Police seized \$200,000 worth of the synthetic drug near Arnprior in the Ottawa area in February.

The drug also sent five people to hospital in the Owen Sound area in January, the Owen Sound Sun-Times reported.

Since the drug isn't illegal in Canada, police can't charge someone for possession, Det. Sgt. Mark Kielb of the Owen Sound police department said.

"These kinds of drugs are really, really dangerous" and longtime effects unknown, Dr. Hazel Lynn, Grey-Bruce's medical officer of health, told the newspaper.

Users' blood pressure shoots up, their heart rate increases, they become severely dehydrated, and as they descend from a quick state of euphoria, hallucinations take hold, she said.

"The hallucinations are very difficult to control. Lightning, fire. They thought they were on fire," she said in a CBC Ontario Morning interview in January.

Toronto health authorities have yet to find a significant problem with the drug in the city, they said.

"We probably were seeing them and didn't know what they were, and our usual drug screens were coming back negative, but we still had a feeling the patient was high on something," Dr. Margaret Thompson of the Ontario Poison Centre cautioned the CBC.

"Methamphetamine and cocaine operate in the brain in completely opposite ways. It would be atypical that both drugs would be taken together, but that's the effect that occurs with bath salts," Louis DeFelice of the Virginia Commonwealth University's School of Medicine said in an American Institute of Physics newsletter.

"Rather than cancel each other, they exacerbate the effect of either drug applied alone," said DeFelice, one of the few scientists who have studied the drug.

The U.S. Senate last Friday passed a bill to ban "synthetic marijuana" that bill sponsor Sen. Charles Schumer of New York said would include "bath salts."

The bill and a U.S. House of Representatives bill will go to a conference committee and could become law shortly.

<http://www.thestar.com/news/article/1203514--bath-salts-designer-drug-prompts-emergency-ban-in-u-s>

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197



Revised NOI and Critical Path for MDPV

Jocelyn Kula to: Johanne Beaulieu

Cc: Tara Phillips, Nathan Isotalo

2012-05-31 01:33 PM

For your review and approval. The NOI has been approved by Legal Services and ORS.



NOI MDPV 2012-05-31 1pm.doc



Critical Path for Scheduling of MDPV May 31 2012.docx

Jocelyn

Jocelyn Kula

Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire

Office of Controlled Substances/ Bureau des substances contrôlées

Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et
de la sécurité des consommateurs

Health Canada/ Santé Canada

Tel: (613) 946-0125 Fax: (613) 946-4224

198

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

Notice to interested parties – Proposed amendment to Schedule I to the *Controlled Drugs and Substances Act*

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's intent to add methylenedioxypropylamphetamine (MDPV), namely 3,4-methylenedioxypropylamphetamine and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule I to the *Controlled Drugs and Substances Act* (CDSA).

MDPV is a synthetic drug that is used for its stimulant-like psychoactive effects. Stimulants in general may significantly increase blood pressure, heart rate and pulse. Adverse physical effects associated with the use of stimulants can include irregular or abnormal heartbeat, heart attack or cardiovascular collapse. There have been reports that MDPV use has also been associated with severe panic attacks and anxiety, as well as hallucinations and psychosis.

Although MDPV is not listed under any of the United Nations drug control conventions, a number of countries have already elected to regulate it as a controlled substance including the United States, Australia, Denmark, Sweden and the United Kingdom.

Health Canada is proposing to include MDPV in Schedule I to the CDSA in order to prohibit the following activities with this substance: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The scheduling of MDPV will also ensure law enforcement can take action under the CDSA against all suspected illegal activities involving MDPV.

This proposed action is in response to concerns expressed by health officials and recent increases in law enforcement and border seizures of products labelled as "bath salts". Such products are not genuine bath salt products intended for softening and/or cleansing the skin, but contain one or more substances with stimulant properties including mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and MDPV. While the extent of their use in Canada is unknown, "bath salt" products are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky".

The publication of this notice begins a 30-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D, 123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. In particular, parties

who believe they are conducting legitimate activities involving MDPV are encouraged to respond to inform Health Canada's decision with respect to regulation of MDPV under the CDSA.

Cathy Sabiston
Director General
Controlled Substances and Tobacco Directorate

Page(s) 000727 to\à 000727

**Is(Are) exempted pursuant to section(s)
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**

Johanne Secombe!

1) Plo put in ^{reflexion} ~~checkbox~~ have legal & suganne also sign off.

200

Handwritten initials/signature

DEPARTMENT OF HEALTH
CONTROLLED DRUGS AND SUBSTANCES ACT

Notice to interested parties – Proposed amendment to Schedule III to the *Controlled Drugs and Substances Act*

This notice provides interested stakeholders with the opportunity to provide comments on Health Canada's intent to add 3,4-methylenedioxypropylvalerone (MDPV) and its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues to Schedule III to the *Controlled Drugs and Substances Act* (CDSA).

MDPV poses a potential risk to the health and safety of Canadians because its use can result in increased blood pressure and increased heart rate, and has also been associated with panic attacks, anxiety, hallucinations, suicidal thoughts and death.

Although MDPV is not listed in the Schedule to any of the United Nations Drug Control Conventions, a number of countries have already elected to regulate it as a controlled substance including the United States, Australia, Denmark, Sweden and the United Kingdom.

Is it on WHO list to be examined? Under H.C.

Health Canada is not aware of any legitimate medical, scientific or industrial applications for MDPV and is therefore not intending to regulate MDPV in accordance with existing regulatory schemes under the CDSA.

This proposed action is in response to recent increases in law enforcement and border seizures of products labelled as "bath salts". Such products are not genuine bath salt products intended for softening/cleansing the skin, but contain one or more substances with stimulant properties including mephedrone and methylone (which are already included in Schedule III to the CDSA as analogues of amphetamine), and MDPV. While the extent of their use in Canada is unknown, "bath salt" products are available for purchase on the Internet and may be found in alternative lifestyle stores. These products may also be labelled as "plant food" and/or "not for human consumption". Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky".

What about N-Sdeath?

H.C. therefore ~~is~~ ^{is proposing to} ~~include~~ ^{include}

Including MDPV in Schedule III to the CDSA would prohibit the following activities with this substance: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The scheduling of MDPV will also ensure law enforcement can take action against all suspected illegal activities involving MDPV.

The publication of this notice begins a 60-day comment period. If you are interested in this process or have comments on this notice, please contact Mr. Nathan Isotalo, Regulatory Policy Division, Office of Controlled Substances, Address Locator: 3503D, 123 Slater St., Ottawa, Ontario, Canada, K1A 0K9, by fax at (613) 946-4224 or by email

at OCS_regulatorypolicy-BSC_politiquereglementaire@hc-sc.gc.ca. In particular, parties involved in legitimate activities involving MDPV are encouraged to respond to inform Health Canada's decision with respect to regulation of MDPV under the CDSA.

CATHY SABISTON

Director General

Controlled Substance and Tobacco Directorate

201

FOR INFORMATION

12-110470-969

MEMORANDUM TO THE MINISTER OF HEALTH

Scheduling of MDPV

SUMMARY

- The purpose of this memorandum is to provide background information in an advance of media event on Tuesday, June 5, 2012, regarding products labelled as "bath salts."
- "Bath salt" products typically contain one or more of the following three chemicals: mephedrone, methylone and methylenedioxypropylamphetamine (MDPV). While mephedrone and methylone are already scheduled under the *Controlled Drugs and Substances Act* (CDSA) by virtue of the fact that they are analogues of amphetamine, MDPV is not yet regulated as a controlled substance in Canada.
- The use of these products has been associated with severe panic attacks and anxiety, as well as hallucinations and psychosis.
- The purpose of the event is to demonstrate that the Government of Canada is taking immediate steps to regulate MDPV as a controlled substance in order to protect the health and safety of Canadians.

BACKGROUND:

A number of recent media articles in both the United States and Canada have highlighted the danger posed by products labelled and marketed as "bath salts." Canadian media reports have originated primarily from eastern provinces, including New Brunswick and Nova Scotia. On May 18, 2012, health officials in northern Nova Scotia issued a warning about "bath salts," including reports of a significant number of emergency room visits. There have also been reports of "bath salts" being used to lace other drugs such as marijuana.

.../2

- 2 -

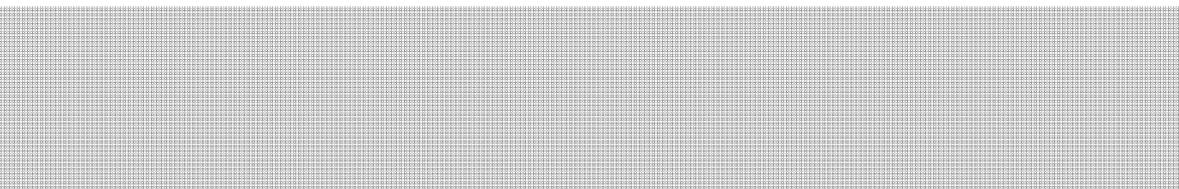
“Bath salts” are available for purchase on the Internet and may be found in alternative lifestyle stores. Examples of product names include “MITSEEZ,” “MOJO Novelty Bath Salts,” “Ivory Snow,” “Purple Wave,” and “Vanilla Sky.” These products may also be labelled as “plant food” and/or “not for human consumption” to circumvent regulatory control.

In the United States, the Drug Enforcement Administration used its emergency scheduling authority to temporarily ban activities with mephedrone, MDPV and methylone in October 2011. Other countries, such as the United Kingdom, have also moved to ban activities with MDPV.

CURRENT STATUS:

Health Canada is taking immediate steps to add MDPV to Schedule I to the CDSA, thereby prohibiting all activities, e.g., importation, exportation, possession, production, rendering all activities with it illegal. The penalties associated with illegal activities involving substances listed in Schedule I are the highest imposed by the CDSA.

The first step in this process is the publication of a Notice to Interested Parties (NOI) that the government proposes to add MDPV to Schedule I of the CDSA. This NOI will be published in the *Canada Gazette*, Part I, on June 9, 2012 and will provide interested stakeholders with a 30-day period to comment on the proposal. In the interim, the Controlled Substances and Tobacco Directorate (CSTD) will continue its work on a comprehensive scheduling assessment of MDPV and the development of a full regulatory proposal for Treasury Board consideration.



CONSIDERATIONS:

While other stimulants are typically included in Schedule III to the CDSA, CSTD is proposing to add MDPV to Schedule I because of the dangers posed by this illicit drug, and the extensive public references to cocaine and amphetamine-like effects. This will ensure that offences involving it are subject to the most serious penalties under the CDSA (i.e. those imposed for activities with substances such as heroin and methamphetamine). Proceeding in this way will also align the scheduling of MDPV with the rescheduling of amphetamines from Schedule III to Schedule I under the *Safe Streets and Communities Act* (Bill C-10), which will come into force at a date to be determined.

s.21(1)(a)

s.21(1)(b)

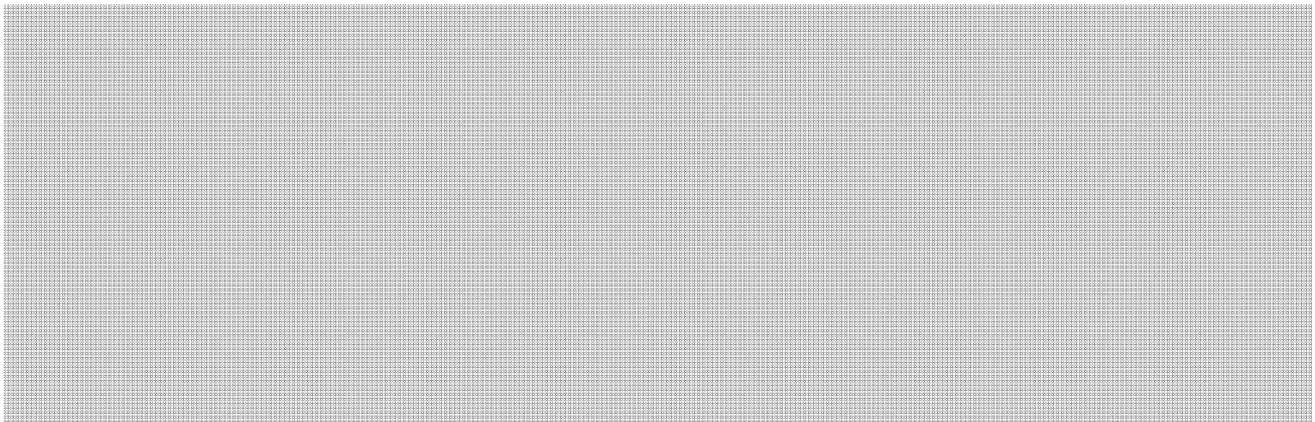
- 3 -

Health Canada's Drug Analysis Service has however identified MDPV in 449 exhibits of suspected controlled substances seized by law enforcement since January 2010.

PORTFOLIO CONSIDERATIONS:

There are no implications for Health Portfolio partners.

NEXT STEPS:



 06/04/12.
Deputy Minister's Office

MECS #12-110470-969

Branch Head: Hilary Geller, ADM, HECSB

Telephone: 613-946-6701

Attachment

Appendix A - Stakeholder List, Invitation, Invitee (Confirmed) and Biography for



s.19(1)

Document created on: June 1, 2012

Appendix A

Stakeholder List

A representative of the Canadian Council on Substance Abuse will also be invited to attend this event.

HECSB is prepared to contact the Canadian Association of Chiefs of Policy [REDACTED] and health officials from northern Nova Scotia (including [REDACTED] Addiction Services, Pictou County) regarding this event, but has not done so in light of the immediacy of the event and the fact that these individuals would have to travel from Nova Scotia.

The Minister's Office has specified that the Minister, M.P. Shelly Glover, and one law enforcement official will speak at the event.

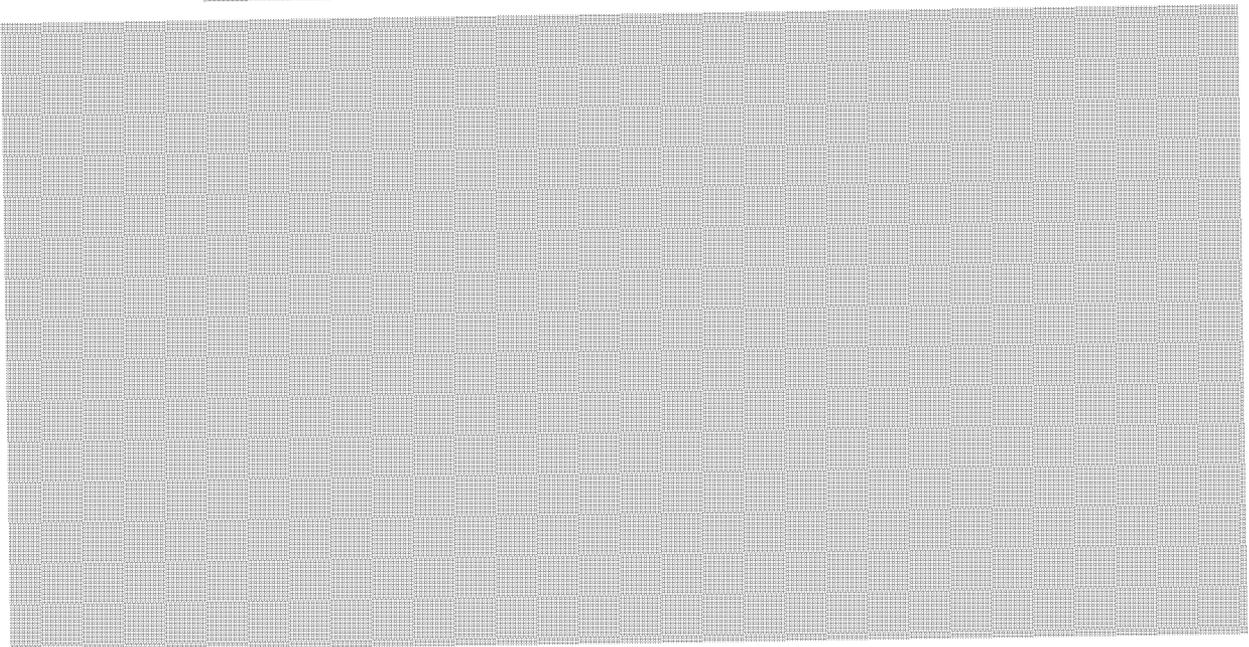
Invitation

Due to time constraints, officials contacted invitees for this event by telephone.

Invitee (Confirmed)

HECSB has confirmed the participation of [REDACTED] Royal Canadian Mounted Police (RCMP), at the event on June 5, 2012.

Biography for [REDACTED]



206



For Your Review: Draft Triage Statement Form (MDPV)

Tara Phillips to: Jocelyn Kula

Cc: Nathan Isotalo

2012-06-04 10:36 AM

Hi Jocelyn,

Please find attached, for your review, a draft Triage Statement Form for the scheduling of MDPV.



Triage Statement MDPV 4-Jun-12.doc

The responses, i.e., the check marks, were discussed a couple of weeks ago with our Treasury Board Secretariat analyst, Kyle Burns; however, a draft has not yet been shared with him.

Thank you,

Tara

207

s.21(1)(a)

s.21(1)(b)

Interim Triage Statement Form

Overall objective: Seeing as regulatory impact analysis can be resource intensive, an early assessment of the expected impacts of regulatory proposals helps determine where approval processes can be streamlined and where analytical resources should be focused.

The Triage Statement facilitates this early assessment and should be completed by departments and agencies at the earliest stages of regulatory design. A draft Triage Statement should be shared with the Regulatory Affairs Sector of the Treasury Board Secretariat in order to determine the overall expected impact (e.g. "low", "medium" or "high") of a regulatory proposal and determine the analytical and other requirements to be met at all stages of the regulatory process.

References: Please consult the Triage Instructions for guidance on completing the Triage Statement Form (Forthcoming). Guidelines and other tools are available at <http://www.tbs-sct.gc.ca/ri-qr/documents/list-liste-eng.asp>.

Section I: Overview

Type of Proposal: Amended Regulation ▼

Title of the Regulatory Proposal:
Regulation Amending Schedule IV to the CDSA to include MDPV
Sponsoring Regulatory Organization(s):
Health Canada
Statutory Authority:
Controlled Drugs and Substances Act
Approximate target month / quarter of submission of regulatory proposal to PCO-OIC:

(RAS Service Standard: 10 business days)

Background

A number of recent media articles in both the United States and Canada have highlighted the danger posed by products labelled and marketed as "bath salts". "Bath salts" typically contain one or more of the following three chemicals: mephedrone, methylone and methylenedioxypyrovalerone (MDPV). While mephedrone and methylone are already scheduled under the *Controlled Drugs and Substances Act* (CDSA) by virtue of the fact that they are analogues of amphetamine, MDPV is not yet regulated as a controlled substance in Canada.

"Bath salts" are available for purchase on the Internet and may be found in alternative lifestyle stores. Examples of product names include "MITSEEZ", "MOJO Novelty Bath Salts", "Ivory Snow", "Purple Wave", and "Vanilla Sky". These products may also be labelled as "plant food" and/or "not for human consumption" to circumvent regulatory control.

Canadian media reports concerning "bath salts" have originated primarily from eastern provinces, including New Brunswick and Nova Scotia. On May 18, 2012, health officials in northern Nova Scotia issued a warning about "bath salts", including reports of a significant number of emergency room visits. There have also been reports of "bath salts" being used to lace other drugs such as marijuana.

In the United States, the Drug Enforcement Administration used its emergency scheduling authority to temporarily ban activities with mephedrone, MDPV and methylone in October 2011. Other countries, such as the United Kingdom, have also moved to ban activities with MDPV.

Issue

MDPV is a central nervous system stimulant. Adverse physical effects associated with the use of stimulants can include palpitations, irregular or abnormal heartbeat, heart attack or cardiovascular collapse. MDPV use has also been associated with severe panic attacks and anxiety, as well as hallucinations and psychosis.

Health Canada has only limited information regarding the occurrence of "bath salts" in Canada, and no information on product uptake or use per se. Health Canada's Drug Analysis Service has however identified MDPV in 449 exhibits of suspected controlled substances seized by law enforcement since January 2010.

Objectives

The primary objective of this regulatory proposal is to protect the health and safety of Canadians by reducing the availability of MDPV in Canada by listing the substance in Schedule I to the CDSA. Scheduling MDPV would respond to concerns expressed by health officials and would enable law enforcement to take action under the CDSA against suspected illegal activities.

Description

This regulatory initiative would add MDPV to Schedule I to the CDSA, which means that all activities including importation, exportation, possession, production, etc., would be illegal. The penalties associated with illegal activities involving substances listed in Schedule I are the highest imposed by the CDSA.

While other stimulants are typically included in Schedule III to the CDSA, this proposal is to add MDPV to Schedule I because of the apparent dangers posed by this emerging drug, and the extensive public references to cocaine and amphetamine-like effects. This will ensure that offences involving MDPV are subject to more serious penalties akin to those associated with other substances in Schedule I such as heroin and methamphetamine. Proceeding in this way will also align the scheduling of MDPV with the rescheduling of amphetamines from Schedule III to Schedule I under the *Safe Streets and Communities Act*, which will come into force at a date yet to be determined.

Key Stakeholders

Law enforcement agencies

Page(s) 000737 to\à 000741

**Is(Are) exempted pursuant to section(s)
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

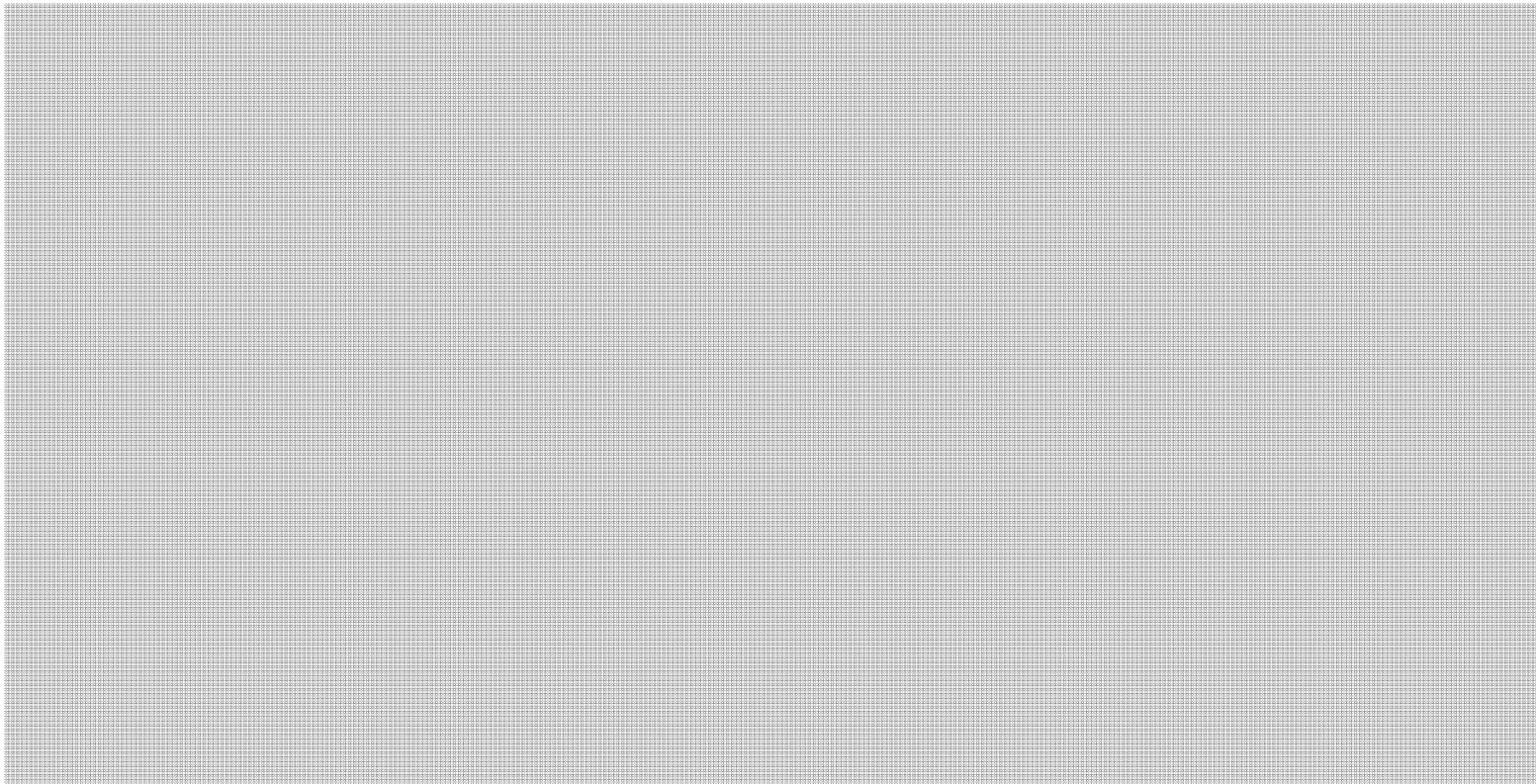
21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**

s.21(1)(a)

s.21(1)(b)

DRAFT June 4, 2012



6. Sign-offs:

Departmental signoff (*Director*): _____ Date: _____

Name and title (print): _____

Name and address of departmental contact person(s): _____

RAS signoff (*analyst*): _____ Date: _____

The regulatory organization should send two signed copies of the final Triage Statement to TBS-RAS. TBS-RAS will then sign the two Triage Statements and return one copy to the regulatory organization.

Regulatory Affairs Sector, Treasury Board of Canada Secretariat
155 Queen Street, Ottawa (ON) K1A 0R5, Canada

Definitions

Administrative costs: Time and resources required to demonstrate compliance with government regulatory requirements in terms of (1) planning, collecting, processing and reporting of information and (2) completing forms and retaining data required by governments. Includes filling out license applications, various forms, finding and compiling data for audits, learning about requirements, etc. Also known as "administrative burden".

Compliance costs: Upfront capital costs as well as ongoing maintenance and training costs that businesses face when complying with a regulation. Includes signage / notifications (when in material form, such as a road sign), training staff, purchasing new equipment or software, maintaining equipment / software, renting additional space, etc. *Should fees and taxes be included?* (Question for the Small Business Lens Working Group)

Small Business: Defined as any business, whether incorporated or not, with under 100 employees OR between \$30,000 and \$5m in annual revenues.

208



Fw: Placement of MDPV in Schedules to the CDSA

Nathan Isotalo to: Evelyn Soo

Cc: Tara Phillips, Jocelyn Kula

2012-06-04 11:12 AM

Hi Evelyn,

Further to your telephone enquiry Friday seeking clarification as to where MDPV was to be scheduled as mentioned, in consideration of recent events, we are now proposing to add MDPV to Schedule I of the CDSA.

The Office of Research and Surveillance has previously informed OCS that MDPV was not considered controlled under the CDSA on the basis that it does not display sufficient structural similarity to the amphetamines and because the listings of pyrovalerone did not include the analogue provision.

MDPV is related to the Schedule IV controlled substance pyrovalerone however, simple possession is not prohibited for Schedule IV substances. Consequently, the NOI shared with ORS proposed Schedule III as MDPV shares a similar structural base structure to cathinone which is on Schedule III and Schedule III has penalties for simple possession though not as severe as those for Schedule I. In this context, upon royal assent of Bill C-10, MDPV would have remained on Schedule III had our proposal remained unchanged.

In consideration of recent events involving MDPV, we are now proposing to add MDPV to Schedule I to ensure that the strictest penalties of Schedule I be adopted for MDPV as recent offences are worthy of more serious penalties.

Should you require any other clarification, please let us know.

Nathan.

Nathan Isotalo
Senior Policy Analyst
RPD-OCS HECS
Health Canada
613-941-1511

211



For your review: Revised Workplan for MDPV
Tara Phillips to: Jocelyn Kula
Cc: Nathan Isotalo

2012-06-04 10:39 PM

Hi Jocelyn,

Please find attached a revised workplan for scheduling MDPV under the CDSA for your review.



DRAFT MDPV WorkPlan June 4, 2012.doc

Thank you,

Tara

WORKPLAN: Scheduling of MDPV under the *Controlled Drugs and Substances Act*

Task/Activity		Target Date	Lead	Status
TRIAGE STATEMENT				
1	Draft triage statement	June 8, 2012	RPD	Ongoing
2	Consult with Treasury Board Secretariat	June 15, 2012	RPD, TBS	Ongoing
3	Obtain Director approval of triage statement	June 22, 2012	RPD, DO	
4	Obtain TBS approval of triage statement	June 29, 2012	RPD, DGO	
NOTICE TO INTERESTED PARTIES (Notice)- for publication in <i>Canada Gazette, Part I</i>				
1	Draft Notice	May 25, 2012	RPD	Complete
2	Obtain Director approval of Notice	May 29, 2012	RPD, DO	Complete
3	Obtain DG, CSTD approval of Notice	May 30, 2012	RPD, DGO	Complete
4	Brief senior management (ADM/DM) on Notice, as required	May 31, 2012	RPD, DGO, ADMO	Complete
5	Submission to Canada Gazette Directorate	June 1, 2012 (minimum 6 working days prior to publication date)	RPD, Canada Gazette Directorate	Complete
6	Publication in <i>Canada Gazette, Part I</i>	June 9, 2012	Canada Gazette Directorate	Ongoing
7	30-day comment period ends	July 10, 2012	RPD	
8	Review and analysis of comments received	July 13, 2012	RPD	

000745

ISSUE ANALYSIS SUMMARY				
1	Research & Analysis (including ORS contract on pharmacology)	June 22, 2012	RPD & ORS	Ongoing
2	Draft Issue Analysis Summary	June 29, 2012	RPD	Ongoing
3	Consultation with internal partners (DAS, ORS, etc.)	July 4, 2012	RPD	
4	Obtain Director, OCS approval of Issue Analysis Summary	July 6, 2012	RPD, DO	
REGULATORY PROPOSAL				
Note: Provided that no legitimate industry is identified via <i>Notice to interested parties</i>, there will be no administrative burden or compliance burden associated with proposal. Therefore, Regulatory Cost Calculator results will not be required.				
I. Preparation of Drafting Instructions				
1	Prepare drafting instructions	June 8, 2012	RPD	
2	Legal Services Review of drafting instructions	June 15, 2012	LSU	
3	Translate drafting instructions	June 22, 2012	RPD	
4	Obtain Director, OCS approval of drafting instructions	June 29, 2012	RPD, DO	
5	Obtain DG, CSTD approval of drafting instructions	July 11, 2012	RPD, DGO	
7	Submit drafting instructions to Department of Justice Drafting Service	July 13, 2012	RPD	

s.21(1)(a)
s.2000746

Page(s) 000747 to\à 000747

**Is(Are) exempted pursuant to section(s)
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

21(1)(a), 21(1)(b)

**of the Access to Information Act
de la Loi sur l'accès à l'information**

213

June 5, 2012



Canadian Centre on Substance Abuse
Centre canadien de lutte contre l'alcoolisme et les toxicomanies

Prepared by CCSA in partnership with the
Canadian Community Epidemiology Network on Drug Use (CCENDU)

CCENDU Drug Alert

"Bath Salts"

Summary Information

- "Bath salts" are not salts that go in your bath, but is rather the street name for a number of synthetic amphetamine-type stimulants that look like salts (i.e., they are a white powder).
- The general public, especially youth, should be aware that although bath salts are often identified as "legal highs" or "not illegal" this **does not** make them safe.
- People taking bath salts report hallucinations, paranoia, chest pain, blurry vision and increased body temperature, and can be agitated and combative.
- Bath salts are sold by dealers via the Internet or in "head-shops."
- As of May 2012 the use of bath salts in Canada appears to be mainly limited to the Maritime provinces.

What are "bath salts"?

Bath salts is a name used for a class of products containing synthetic stimulants sold by dealers via the Internet or in drug paraphernalia shops ("head-shops"). Bath salts are frequently labelled "not for human consumption," presumably in an attempt to circumvent drug laws in the jurisdictions in which these products are purchased.

These products are in no way related to the salts that are sold to put in the bath (e.g., Epsom salts or other perfumed skin softening agents). Rather, they contain amphetamine-type stimulants, such as methylenedioxypyrovalerone (MDPV), methylone or mephedrone. These substances are part of the group of drugs known as synthetic cathinones. Synthetic cathinones are prepared in illicit laboratories and are chemically similar to naturally occurring cathinones found in the Khat plant, a shrub native to the Horn of Africa and the Arabian Peninsula.

Individuals under the influence of these substances report hallucinations, paranoia, chest pain and blurry vision, and appear agitated and combative. Because of this agitation, there have been some reports from the United States that these individuals can pose a danger to themselves and others.

Street names

Ivory Wave, Vanilla Sky, Pure Ivory, Cloud Nine, Whack, Bolivian Bath, Purple Wave, Charge+, Ocean Burst, Ecstasy, Gloom, Purple Rain, Salt, Fly, Hurricane Charley, Crash, White, Rush, Plant Food, Bubbles, Meow Meow, Explosion, Monkey Dust, Monkey Mess, Monkey Mash, Pixie Dust, Rave On.

CCENDU DRUG ALERT

Reports from CCENDU

Reports from the Maritime provinces indicate that authorities there are witnessing an increased presence of bath salts. The state of Maine recently experienced an increased prevalence of this synthetic drug (see the article in the *Bangor Daily News*), which may be related to the increased presence in the Maritime provinces.

The following information was compiled in response to a request for information sent out to CCENDU on May 3, 2012. Information was received between May 3 and May 22, 2012. A summary of the findings is presented in Table 1.

Level of Concern

Level of Concern is assessed by the individual compiling the information received by the network. There are currently no established definitions used to determine level of concern.

Table 1. Level of concern regarding the use of bath salts among Canadian municipalities (ordered from west to east) based on local reports between May 3 and May 22, 2012.



2 in Calgary now

Level of Concern	City	Notes
	Vancouver	No reports
	Edmonton	No reports 1 <i>nd</i>
	Prince Albert	Two cases of self-disclosed use of bath salts in the fall of 2011. Detox and outpatient facilities report people talking about bath salts, but no confirmed use.
	Winnipeg	Report of a few individuals claiming to have used bath salts irregularly when they were unable to obtain other drugs; however, nothing has been confirmed.
	Toronto	There is little to report in Toronto specific to MDPV. It is one of many "research chemicals" used among youth in Toronto's club and party scene. Use of these drugs is still limited, although growing. Data about local use of research chemicals are non-existent and reports are anecdotal. The most complete information comes from the TRIP Project, a harm reduction program working with youth in the club and party scene. TRIP has begun using test kits to see what pills actually contain. A TRIP staff member, who is also a member of Toronto's Research Group on Drug Use, noted that "the last pressed E pill tested by a volunteer came out positive for cathinones and piperazines." For more information, see TRIP's website: http://www.tripproject.ca/trip/?q=node/2005 . At the provincial level, the 2011 Ontario student survey (OSDUHS) assessed the reported use of mephedrone or bath salts among students in grades 7 to 12. However, the estimates were suppressed because they were too low to estimate with the sample of 9,000. The Centre for Addiction and Mental Health (CAMH) has concluded that there is no evidence that mephedrone had measurably diffused to the student population.
	Ottawa	Neither treatment providers nor the police report encountering "bath salts." However, there is an expectation among some that areas of the Ottawa Valley could be seeing bath salts in the near future. This expectation is due to a seizure of bath salts by the Ontario Provincial Police in the neighbouring community of Arnprior.
	Montreal	No reports

CCENDU DRUG ALERT



New
Glasgow, NS

In April New Glasgow police reported a few cases of individuals acting erratically and posing a danger to themselves as a result of using bath salts. Local health authorities have reported at least fourteen (14) incidents related to bath salts in the past few months. These include cases reported by hospital emergency departments in New Glasgow and Truro, where individuals ingesting bath salts required emergency care. These incidences also include calls and admissions to local withdrawal management centres. Local authorities have found bath salts mixed with other drugs such as cannabis, so there is great concern that users may be unaware they are ingesting the substance. The Pictou County Health Authority has been meeting with local law enforcement to discuss the emergence of bath salts and discuss demand reduction and supply reduction strategies.

Legal Status in Canada

Mephedrone and methyldone are regulated as controlled substances in Canada because they are deemed to be similar to amphetamine, which is listed as Item I in Schedule III of the *Controlled Drugs and Substances Act* (CDSA). MDPV is not however considered to be a controlled substance and so is not currently subject to the controls set out in the CDSA or its regulations.

Update: June 5, 2012

The Government of Canada plans to make MDPV illegal this fall by placing it on Schedule I of the CDSA, in the same category as heroin and cocaine. The new rules mean activities such as possession, trafficking, possession for the purpose of trafficking, importation, exportation and production will be illegal unless authorized by regulation.

Resources

A comprehensive source of information on bath salts is provided in a webinar produced by the Northern New England Poison Center in August 2011. This webinar, which provides information for both prevention and healthcare professionals, is available at: <http://www.nnepc.org/poison-prevention-education/lectures/bath-salt-webinar>.

CCENDU will continue to monitor the use of bath salts across Canada, as well as internationally. If you have any questions, comments, information to contribute or corrections to the information contained in this alert, please contact CCENDU@ccsa.ca.

The Canadian Community Epidemiology Network on Drug Use (CCENDU) is a nation-wide network of community level partners who share information about local trends and emerging issues in substance use and exchange knowledge and tools to support more effective data collection.

The Canadian Centre on Substance Abuse (CCSA) provides national leadership, develops sustainable partnerships and advances solutions to ensure that all people in Canada live in a healthy society free of alcohol- and other drug-related harm.

Disclaimer: Though every effort has been made to identify and compile the best and most reliable information available on the topic, the nature of the alert is such that CCSA cannot confirm the validity of all information included or that acquired from links provided. While we have done our utmost to provide correct information, CCSA makes no representations or warranties of any kind, express or implied, about the completeness, accuracy or reliability with respect to the information included in this alert or the information included in the links provided.

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000750

214



RE: Seizure of MDPV
Loo, Paul-B to: 'Tara Phillips'
Cc: Nathan Isotalo

2012-06-05 02:43 PM

Working on it. Should have a confirmed answer by tomorrow. Current belief is that the shipment was destroyed by the RCMP...

Paul

From: Tara Phillips [mailto:tara.phillips@hc-sc.gc.ca]
Sent: June-05-12 2:02 PM
To: Loo, Paul-B
Cc: Nathan Isotalo
Subject: Seizure of MDPV

Hi Paul,

Further to our discussion of yesterday concerning a seized shipment of MDPV in early 2011, I have attached a scanned piece of correspondence that will hopefully be helpful to you in identifying the shipment in question.

My Director General has asked me to find out what the ultimate conclusion of this situation was and, specifically, whether or not the shipment was returned.

Let me know if you have any questions or require additional information.

Thank you,

Tara

Tara Phillips
Regulatory Policy Division / Division des politiques réglementaires
Office of Controlled Substances /
Bureau des substances contrôlées
Health Canada / Santé Canada
Tel/Tél : 613-946-6521
Fax/Télécopieur : 613-946-4224
Email / Courriel : tara.phillips@hc-sc.gc.ca

Attached Image

0905-311A-CANNON6075MFP

to: tara phillips

2012-06-05 11:49 AM

217



Fw: FW:
Jocelyn Kula to: Nathan Isotalo
Cc: Tara Phillips

2012-06-06 03:16 PM

first set of data from NS

Jocelyn Kula
Manager, Regulatory Policy Division/ Gestionnaire, Division de la politique réglementaire
Office of Controlled Substances/ Bureau des substances contrôlées
Healthy Environments and Consumer Safety Branch/ Direction générale de la santé environnementale et de la sécurité des consommateurs
Health Canada/ Santé Canada
Tel: (613) 946-0125 Fax: (613) 946-4224
----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2012-06-06 03:16 PM -----

From: [REDACTED]
To: 'Jocelyn Kula' <jocelyn.kula@hc-sc.gc.ca>
Date: 2012-06-06 08:47 AM
Subject: FW:

From: [REDACTED]
Sent: Thursday, May 31, 2012 1:39 PM
To: 'jocelyn.kula@hc-gc.ca'
Subject:

s.19(1)

Hi Jocelyn

Didn't know if you had this article but thought you would want it if you didn't

All the best



[REDACTED] BathsaltsCTspiller.pdf

218

Clinical Toxicology (2011), 49, 499–505
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POISONS CENTRE

Clinical experience with and analytical confirmation of “bath salts” and “legal highs” (synthetic cathinones) in the United States

HENRY A. SPILLER¹, MARK L. RYAN², ROBERT G. WESTON³, and JOANNE JANSEN⁴

¹Kentucky Regional Poison Center, Louisville, KY, USA

²Louisiana Poison Center, Shreveport, LA, USA

³Oklahoma State Bureau of Investigation, Edmond, OK, USA

⁴Sullivan University, College of Pharmacy, Louisville, KY, USA

Recently, there has been a worldwide rise in the popularity and abuse of synthetic cathinones. In 2009 and 2010, a significant rise in the abuse of a new group of synthetic cathinones was reported in Western Europe. In 2010, the rapid emergence of a new drug of abuse, referred to as bath salts or “legal high,” occurred in the USA. The growing number of cases along with the alarming severity of the effects caused by the abuse of these substances prompted significant concern from both healthcare providers and legal authorities. We report the experience of the first 8 months of two regional poison centers after the emergence of a new group of substances of abuse. **Method.** This was a retrospective case series of patients reported to two poison centers with exposures to bath salts. Additionally, 15 “product samples” were obtained and analyzed for drug content using GC/MS. **Results.** There were 236 patients of which 184 (78%) were male. Age range was 16–64 years (mean 29 years, SD 9.4). All cases were intentional abuse. There were 37 separate “brand” names identified. **Clinical effects** were primarily neurological and cardiovascular and included: agitation (n = 194), combative behavior (n = 134), tachycardia (n = 132), hallucinations (n = 94), paranoia (n = 86), confusion (n = 83), chest pain (n = 40), myoclonus (n = 45), hypertension (n = 41), mydriasis (n = 31), CPK elevations (n = 22), hypokalemia (n = 10), and blurred vision (n = 7). **Severe medical outcomes** included death (n = 1), major (n = 8), and moderate (n = 130). Therapies included benzodiazepines (n = 125), antipsychotics (n = 47), and propofol (n = 10). **Primary dispositions** of patients were: 116 (49%) treated and released from ED, 50 (21%) admitted to critical care, 29 (12%) admitted to psych, and 28 (12%) lost to follow up. Nineteen patients had blood and/or urine analyzed using GC/MS. MDPV was detected in 13 of 17 live patients (range 24–241 ng/mL, mean 58 ng/mL). The four samples with no drug detected, reported last use of bath salts >20 h prior to presentation. Three of five patients had MDPV detected in urine (range 34–1386 ng/mL, mean 856 ng/mL). No mephedrone or methylone was detected in any sample. **Quantitative analysis performed on postmortem samples** detected MDPV in blood at 170 ng/mL and in urine at 1400 ng/mL. No other synthetic cathinones were detected. **Discussion.** This is the first report of MDPV exposures with quantitative blood level confirmation. Clinical effects displayed a sympathomimetic syndrome, including psychotic episodes often requiring sedation, movement disorders, and tachycardia. Within 8 months of their appearance, 16 states had added synthetic cathinones to the controlled substances list as a Schedule I drug. **Conclusion.** We report the emergence of a new group of substances of abuse in the USA, known as bath salts, with quantitative results in 18 patients. State and federal authorities used timely information from poison centers on the bath salt outbreak during investigations to help track the extent of use and the effects occurring from these new drugs. Close collaboration between state authorities and poison centers enhanced a rapid response, including legislation.

Keywords Synthetic cathinone; Designer drugs; Stimulants; Sympathomimetic syndrome; Drugs of abuse

Introduction

Recently, there has been a worldwide rise in the popularity and abuse of synthetic cathinones. Abuse of one synthetic cathinone – methcathinone – occurred for several decades in the former Soviet Union, Russia, and Eastern Europe and spread to the West in the 1990s.^{1–3} Methcathinone report-

edly had been developed in the former Soviet Union as an antidepressant in the 1930s and separately developed in the West in the 1950s as an appetite suppressant, but was never marketed due to its strong addictive potential. In 2009 and 2010, a significant rise in the abuse of a new group of synthetic cathinones was reported in Western Europe.^{4–11} In 2010, the first cases of exposure to products marketed as “legal highs” and bath salts were reported to US poison centers. Based on the increased use in Europe and availability on the Internet for similar “legal highs,” these products were believed to contain various synthetic cathinones, including mephedrone (4-methylenemethcathinone), MDPV

Received 27 April 2011; accepted 19 May 2011.

Address correspondence to Henry A. Spiller, MS, DABAT, FAACT, Kentucky Regional Poison Center, PO Box 35070, Louisville, KY 40232-5070, USA. E-mail: henry.spiller@nortonhealthcare.org

(methylenedioxypropylvalerone), methylone (3,4-methylenedioxy-N-methylcathinone), methedrone (4-methoxymethylcathinone), and fluoromethylcathinone.^{12,13} The product packages were labeled as bath salts, insect repellants, stain removers, and plant food. However, the users of these products openly spoke of using them as “legal methamphetamine” or “legal cocaine.” The product labels did not provide any indication of the true active ingredients. Unlike the European experience, where many of the products were being purchased from a “dealer” or over the Internet, in the USA the majority of the new “bath salt” products were being purchased locally in small independent stores, such as gas stations, smoke shops, and “head shops.” The growing number of cases along with the alarming severity of the effects caused by the abuse of these substances prompted significant concern from both healthcare providers and legal authorities. During this period in 2010, there was limited information about what these “products” actually contained or the clinical effects that would be expected from abuse of these substances. We report the experience of the first 8 months of two regional poison centers after the emergence of a new group of substances of abuse.

Methods

A retrospective search was performed at two poison centers for all records involving what came to be known as bath salts, for the period January 2010 through February 2011. An initial search was performed to locate any case with a substance name listed as bath salts, insect repellent, stain remover, plant food, MDPV, mephedrone, methylone, cathinones, white lightning, zoom, blue silk, red dove, ivory wave, white cloud, cloud 9, cloud 10, dynamite, or unknown drug. Poison center case notes were then reviewed to verify if there was documentation that the substances involved an illicit “bath salt” case. In November 2010, both poison centers had agreed to code all these exposures under the term “bath salts”. Product names and descriptions were obtained from the documentation in the case notes. Both centers utilize the electronic medical record system Toxicall, which allows review of the record stripped of personal identifiers. All charts were then reviewed by the investigators to verify the substance from the case notes. Calls were received from both the general public and hospitals/healthcare facilities. Toxicall allows storage of all calls and consultations on a specific patient in a single medical record, so that each case involved in this study was included only once, despite multiple calls and consultations of many of these patients. Data obtained included age, gender, substance involved, reason for exposure, history of use if obtained, clinical effects, pertinent laboratory values, therapies administered, and medical outcome. Medical outcome designation was the standard American Association of Poison Control Center categories utilized by poison centers.¹⁴ In a number of cases, because of the confused, agitated, or delusional mental state of the patient, the history of use and any previous abuse history were obtained from significant others of the patient.

During December 2010, because of the lack of information on the contents of these new “products,” 15 products in

their sealed original containers were obtained from separate commercial locations (stores) in the two states for analysis of content.

Blood/serum and/or urine waste samples were obtained from 18 patients for analysis as an initial effort to discover what substances might be involved in the toxidrome displayed by the patients. This was part of a public health response to what was considered as an outbreak of a newly emergent substance of abuse. All samples were obtained during initial patient presentation and examination in the emergency department and were obtained after initial clinical use (if any) had been performed.

Chemicals and reagents

Analytical reference standards for MDPV, mephedrone, methcathinone, and phencyclidine (the latter two used for internal standards) were obtained from Cerilliant. MDPV was received as the powdered HCl salt. A 1 mg/mL (calculated as the free base) stock solution was prepared from this solution by dissolving 11.3 mg MDPV HCl in 10 mL DI water. Mephedrone, methcathinone, and phencyclidine were received as 1 mg/mL solutions. Blank blood was donated by a local blood bank and determined to be drug free by GC/MS analysis.

Analysis of purchased products

After dissolution in methanol, the products were each analyzed using an Agilent 7890A gas chromatograph coupled to an Agilent 5975C mass spectrometer. The column was an Agilent DB-1 (100% dimethylpolysiloxane) (12 m × 0.2 mm × 0.33 μm). Ultra-pure helium was used as the mobile phase using a constant flow of 0.80 mL/min. Other instrumental parameters included: 1 μL injection, split ratio 300:1, injection port 290°C, oven program 100°C for 15 sec, ramped at 65°C/min to 220°C, then at 40°C to 290 with a final hold time of 6.15 min. The total analysis time was 10 min. The mass spectrometer was programmed with a transfer line temperature of 290°C, source temperature of 230°C, quadrupole temperature of 150°C, solvent delay of 0.85 min, and was operated in scan mode from 50 to 550 m/z for the duration of data collection. Identification of the substances present in the bath salts was determined by retention time and mass spectral comparison of the GC/MS data to known standards.

Quantitation of biological specimens

For the quantitation of the bath salt drugs in biological specimens, methcathinone and phencyclidine were used as internal standards. The internal standard solution was made by combining 25 μL aliquots of the 1 mg/mL methcathinone and phencyclidine standards and diluting to 25 mL with DI water, resulting in a 1 μg/mL solution for each drug. Similarly, a 1 μg/mL solution containing both mephedrone and MDPV was prepared by diluting 25 μL of each of the 1 mg/mL solutions to 25 mL DI water.

Mephedrone and MDPV calibrators with concentrations of 25, 50, 75, 100, and 150 ng/mL were prepared by pipetting

appropriate volumes of 1 µg/mL solution into 1 mL aliquots of blank blood obtained from a local blood bank and determined to be drug free by GC/MS analysis.

Sample preparation

The calibrators, 1 mL aliquots of biological specimens, and a 1 mL aliquot of blank blood were pipetted into culture tubes and then extracted using the following procedure. Internal standard (50 µL) was added to each sample, followed by 1 mL of borate buffer. After briefly mixing the samples by vortex, 4 mL of n-butyl chloride was added to each sample. Each tube was capped and shaken for 2 min, followed by centrifugation at 3000 rpm for 3 min. After transferring the resulting organic layer to a 5-mL conical centrifuge tube, 2 mL of 1.0 N HCl was added. The conical tubes were capped and placed on a rotary extractor for 15 min, followed by another 3 min centrifugation at 3000 rpm. The organic layer was discarded. Seven drops (approximately 350 µL) of conc. NH₄OH was added to each to basify the aqueous solution. Chloroform (75 µL) was added, and the samples were capped, shaken for 2 min, and centrifuged again at 3000 rpm for 3 min. The resultant chloroform layer was transferred into autosampler vials and then analyzed by GC/MS.

Analysis

Determination of blood concentration and/or urine concentration was performed using another Agilent 7890A/5975C GC/MS. This instrument was equipped with a DB-1 column having dimensions of 30 m × 0.320 mm × 0.25 µm. For biological samples, 2 µL of extract was injected in splitless mode. Other instrumental parameters: injection port 250°C, ultra-pure helium column flow 1.788 mL/min, oven initial temperature 60°C for 1 min, then 15°C/min ramp to 300°C with a hold time of 3 min, total run time 20 min. The mass spectrometer transfer line, source, and quadrupole temperatures were 280, 230, and 150°C, respectively. The mass spectrometer scanned from 40 to 400 m/z after a solvent delay of 3 min.

Results

The first case was reported in August 2010 in Kentucky and the first case in Louisiana occurred in September 2010. From August 2010 through February 2011, there were 236 patients with a rapid escalation in the number patients reported after November 2010 (see Fig. 1). The majority of patients (n = 184, 78%) were male. The age range was from 16 to 64 years (mean 29 years, SD 9.4). All cases reported the reason for exposure as intentional abuse. Where history was available, a large number of cases reported previous abuse of methamphetamine and/or cocaine and the use of bath salts as a "legal" replacement for these substances. Results from qualitative urine drug screens were recorded in 44 patients and detected positive results for amphetamines, barbiturates, benzodiazepines, caffeine, cannabinoids, cocaine, MDMA, methadone, opiates, oxycodone, and oxymorphone. There were 39 separate "brand" names identified from patient histories (Table 1). In 72% of cases, the originating contact

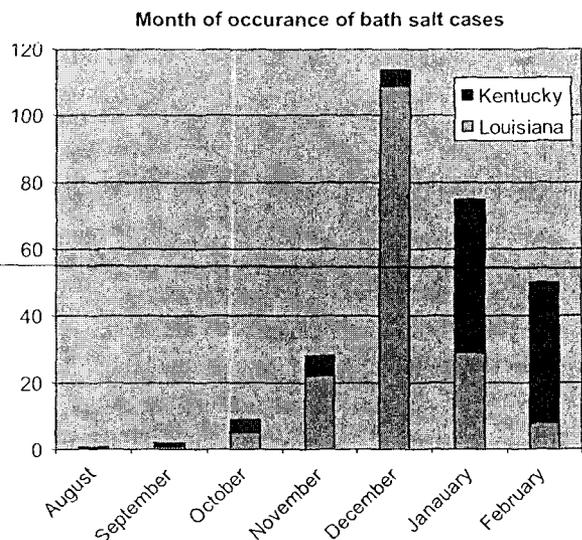


Fig. 1. Month of occurrence of synthetic cathinone cases by state (see colour version of this figure online).

call was from the hospital, with 6% originating from EMS/ambulance service and 22% from the public.

Clinical effects were primarily neurological and cardiovascular and are reported in Table 2. Severe medical outcomes included: death (n = 1), major (n = 8), and moderate (n = 130). The single fatality occurred in a 21-year-old male from a self-inflicted gunshot after an active delusional episode witnessed by family members. A number of alarming and dangerous behaviors (to either self or others) were reported in these patients in temporal association with acute use of large amounts or prolonged use of "bath salts" over several days to several weeks. Examples of these new onset behaviors in separate patients included: jumping out of a window to flee from non-existent pursuers; requiring electrical shock (Taser) and eight responders to initially subdue the patient; repeatedly firing guns out of the house windows at "strangers" who were not there; walking into a river in January to look for a friend who was not there; leaving a 2-year-old daughter in the middle of a highway because she had demons; climbing into the attic of the home with a gun to kill demons that were hiding there, and breaking all the windows in a house and wandering barefoot through the broken glass.

Therapies were primarily sedation and treatment for persistent myoclonus and included the benzodiazepines diazepam, lorazepam, and/or midazolam (n = 125, 53%), the antipsychotics haloperidol and ziprasidone (n = 47, 20%), propofol (n = 10, 4%), and diphenhydramine (n = 2, 1%). The dispositions of patients were: 116 (49%) treated and released from the emergency department, 50 (21%) admitted to a critical care unit, 29 (12%) admitted to behavioral health/psychiatry, 28 (12%) were lost to follow up, and 13 (6%) were managed at a non-healthcare facility.

Eighteen live patients had blood and/or urine analyzed using GC/MS. MDPV was detected in the blood/serum of 13 of 17 patients (range 24–241 ng/mL, mean 58 ng/mL).

Table 1. Names of products reported by users.

Product name	Frequency of reports
Artic blasting station	1
Atomic	1
Bayou revitalisant	1
Blaze	1
Blitz	2
Blue moon	1
Blue silk	5
Bohemian bath salts	2
Bolivian bath salts	2
Dr. booga shooga	3
Cloud 9	73
Cloud 10	2
Columbian odorizer	1
Cotton cloud	4
Dream	1
Dynamite	1
Euphoria	1
Hurricane charlie	1
Ivory wave	9
Ivory wave ultra	1
Kush blitz	1
Lady bubbles	2
Legal	2
Love potion 69	2
Moon dust	4
Night cap	1
NRG-1	1
Q concentrated	1
Red dove	1
Resin	1
Scar face	1
Serenity	1
Super clean stain remover	1
White cloud	1
White diamonds	2
White dove	1
White girls bath salts	1
White lightening	24
Zoom	6

The four samples with no synthetic cathinone detected, reported last use of bath salts >20 h prior to presentation. Additional drugs detected in the blood/serum included citalopram, diazepam, diphenhydramine, hydrocodone, and zolpidem. Three of five patients had MDPV detected in urine (range 34–1386 ng/mL, mean 856 ng/mL). Additional drugs detected in the urine were alprazolam, citalopram, diphenhydramine, hydrocodone, and methamphetamine. No mephedrone or methylone was detected in any sample. Ethanol detection was not included in analysis. Quantitative analysis was performed on postmortem samples in the single fatality. MDPV was detected in blood at 170 ng/mL and in urine at 1400 ng/mL. No other synthetic cathinones were detected.

Fifteen products in their sealed original containers were obtained from separate locations in the two states. The products contained one or more of three of the known synthetic cathinones: 4-methylmethcathinone (mephedrone), methylenedioxypyrovalerone (MDPV), or 4-methylenedioxy-N-methylcathinone

(methylone). Additional substances found included caffeine and an unidentified substance (see Table 3).

Discussion

We report the largest series of synthetic cathinone exposures with a number of important features, including a high incidence of new onset severe neurological/psychiatric changes; qualitative results of the contents of “bath salts”; and quantitative results of blood and urine in synthetic cathinone users.

Previous reports of synthetic cathinone use/abuse have focused primarily on mephedrone and have reported clinical effects consistent with a sympathomimetic syndrome, including tachycardia, agitation, hypertension, palpitations, chest pain, confusion, paranoia, hallucinations, violent behavior, and seizure.^{4–6,8} Our results are consistent with these previous reports. However, in our case series, we found aggressive violent behavior, hallucinations, and paranoia in higher percentages than previously reported. It is interesting to note that the high incidence of neurological/psychiatric changes occurred in a population that had pre-existing experience in illicit stimulant abuse, such as cocaine and methamphetamine, who had not previously reported episodes of neurological/psychiatric changes of such severity. The increased incidence may have occurred for a number of reasons. Experience with misuse/abuse of this drug is limited. While the reported incidence pattern is different from previous reports of synthetic cathinone abuse, the clinical effects reported are similar, and this may simply be a reflection of a difference in dosing patterns or patient populations (e.g. “club” drug use vs. street drug abuse). Another possibility is that this may represent a difference in clinical patterns from the individual synthetic cathinones, perhaps based on subtle differences in the effects on neurotransmitters.^{15–17} The previous reports from the European experience primarily involved mephedrone. However, in our case series, all verified serum or urine samples contained MDPV, with no detected mephedrone or methylone. This second possibility should be viewed with caution as only 6% of patients in our series had laboratory verification of their exposure. Movement disorders may also be a differentiating factor. A previously unreported finding in our series was myoclonus in 19% of the patients and elevated CPK in 9% of the patients. One report of “ivory wave” exposure, which may have involved MDPV, reported involuntary facial contortions, supporting a possible movement disorder as a clinical effect with MDPV abuse.¹⁸ Previous reports of a parkinsonian syndrome associated with methcathinone have been attributed to a manganese contamination during illicit preparation of the drug.^{1,2}

Analysis of the “legal high” or “bath salt” products revealed a combination of three synthetic cathinones: mephedrone, methylone, and MDPV. This is similar to the European experience, with some differences.^{12,19} In the USA, the primary synthetic cathinone available was not mephedrone, and the main distribution point was through small local stores. We believe that the wide availability, coupled with the ease of anonymous local purchase and inexpensive

Table 2. Reported clinical effects.

Clinical effect	No. of patients with reported effect (% of total patient group)	Comments
Agitation	194 (82%)	Mean heart rate for those with reported tachycardia was 124 (SD 15.5) with a range of 100–178 beats per minute
Combative violent behavior	134 (57%)	
Tachycardia	132 (56%)	
Hallucinations	94 (40%)	Mean reported CPK elevation was 1825 U/L with a range of 301–4400 U/L Mean reported potassium for those with hypokalemia was 2.9 mEq/L with a range of 2.1–3.4 mEq/L
Paranoia	86 (36%)	
Confusion	83 (34%)	
Myoclonus	45 (19%)	
Hypertension	41 (17%)	
Chest pain	40 (17%)	
Mydriasis	31 (13%)	
CPK elevations	22 (9%)	
Hypokalemia	10 (4%)	
Blurred vision	7 (3%)	
Catatonia	1 (1%)	

Definitions: Tachycardia was a heart rate >99 bpm; hypertension was systolic pressure >170 mmHg or diastolic pressure >90 mmHg; hypokalemia K <3.5 mEq/L, CK elevation CPK >250 U/L.

products, allowed a rapid expansion of these drugs into the market. In many cases, they were easier to obtain than beer or cigarettes. Additionally, no ingredients were listed on the packaging. Unlike web sites that may allude to ingredients that the knowledgeable prospective customer might recognize and/or desire, the bath salt products were primarily sold in small stores by clerks with little or no knowledge of what the product might contain. Analysis of two “brand names” (white lightening and dynamite), which were obtained at different locations, revealed different synthetic cathinones as the primary ingredient, despite similar appearing packaging. The 15 products analyzed and reported here were purchased in December 2010 and may not represent the psychoactive substances in future “bath salt” or “legal high” products. A wide variety of novel psychoactive substances are available and may replace the substances detected in the present group of products.^{12,24}

Quantitative analysis showed serum levels of 24–241 ng/mL of MPV. Previous serum MDPV concentrations in live patients have not been reported, but these concentrations are in the range of the mephedrone level (0.15 mg/L) reported by Wood et al.²⁰ A limitation of interpreting these blood/serum levels of MDPV is that the time from use of the drug to the time of obtaining the sample is not known. We believe this is the first report of postmortem quantitative MDPV concentrations. Postmortem concentrations in five fatalities associated with another synthetic cathinone, mephedrone, ranged from 0.13 to 5.1 mg/L.^{4,5} Urine concentrations after abuse of MDPV have recently been reported in Finland in a group of opioid-dependent patients undergoing opioid substitution therapy.²¹ The similarities between our patient group and the report by Ojanpera et al. were the reported use of MDPV as a substitute for illicit amphetamine and similar urine concentrations. This suggests that urine may be a useful medium to detect previous MDPV abuse.

Table 3. Ingredients detected in “bath salt” samples.

Product name	Drug found	Labeled “use”	Physical appearance
White lightening	Mephedrone	Insect repellent	White dry powder
White lightening	MDPV	Natural stain remover	White dry powder
Zoom	MDPV	Bath salt	Beige powder
Energizing aromatherapy powder	MDPV and caffeine	Potpouri	Beige powder
Euphoria	Methylone and caffeine	Bath salt	Beige powder
Cotton cloud	Mephedrone, methylone, and MDPV	Bath salt	White crystalline powder
Cloud 9	Methylone and MDPV	Bath salt	Beige powder
Bayou ivory flower	Mephedrone	Bath salt	Beige powder
Cloud 10	MDPV	Not on product	Beige powder
White dove	Methylone	Bath salt	Beige powder
Dynamite	Methylone	Bath salt	White dry powder
Dynamite “plus”	MDPV	Bath salt	Beige powder
White china	MDPV and unknown compound	Bath salt	Beige powder
Snow day	Methylone and MDPV	Bath salt	Beige powder
Bolivian bath salts (scarface)	MDPV	Bath salt	White dry powder

Little is known of the mechanism of action of synthetic cathinones, but a clinical picture of a sympathomimetic syndrome has become evident. Methcathinone and methylone appear to inhibit membrane catecholamine transporters, suggesting a reuptake inhibition. Comparison of methcathinone and methylone to methamphetamine and methylenedioxymethamphetamine (MDMA) showed similar effects on dopamine and norepinephrine reuptake inhibition, but methylone with its 3,4-methylenedioxy group showed increased serotonin reuptake inhibition.¹⁵ Animal studies with methylone showed potent monoamine release effects for dopamine and serotonin and less so for norepinephrine, and reflected reuptake inhibition of dopamine, norepinephrine, and serotonin.¹⁶ In a mouse model, MDPV increased dopamine concentrations but did not appear to affect serotonin concentrations.¹⁷ While the mechanism is not yet fully elucidated, it appears that the behavioral toxicity (including self-injurious behavior and schizophrenic-like psychoses) and movement disorders of synthetic cathinones may have a dopaminergic mechanism similar to amphetamines.^{22,23}

Within 8 months of their appearance on the US market, more than 1400 cases of misuse and abuse of "bath salts" had been reported to US poison centers in 47 of 50 states. On 6 January 2011, Louisiana passed an emergency rule placing six synthetic cathinones in Schedule I. The substances banned were 3,4-methylenedioxymethcathinone (methylone), 3,4-methylenedioxypropylone (MDPV), 4-methylmethcathinone (mephedrone), 4-methoxymethcathinone (methedrone), 3-fluoromethcathinone, and 4-fluoromethcathinone (flephedrone). The number of cases reported in Louisiana decreased dramatically after the ban was put in place on 6 January 2011 (Fig. 1). Within 3 months of this, 15 more states added synthetic cathinones to the controlled substances list as Schedule I drugs, either through temporary emergency rule or direct legislation (Kentucky, Alabama, Arkansas, Florida, Hawaii, Illinois, Idaho, Mississippi, North Dakota, Oregon, Utah, Virginia, Washington, Wisconsin, and Wyoming). Legislation is pending in a number of additional states. Timely information from poison centers on the bath salt outbreak was used by state and federal authorities during investigations to help track the extent of use and effects occurring from these new drugs. Close collaboration between state authorities and poison centers enhanced a rapid response, including legislation.

Conclusion

We report the emergence of a new group of substances of abuse in the USA, known as bath salts, with quantitative results of MDPV use in 19 patients. Calls to US poison centers as a result of the use and abuse of these drugs were first noted in 2010. Rapid analysis and identification of the synthetic cathinones involved in these substances as well as the coordinated response by two poison control centers have permitted a picture of this new epidemic to be presented. The growing number of cases together with the alarming severity of the effects caused by the abuse

of these substances prompted significant concern from both healthcare providers and legal authorities. Since the emergence of these bath salts, a growing number of states have designated six synthetic cathinones as Schedule I controlled substances. However, there are a large number of potential novel psychoactive "designer" drugs that may possibly be distributed in the future.²⁴ Changes to specific moieties may not be addressed in the current legislation, leaving clinical toxicologists, poison centers, and emergency physicians to face an on-going pattern of chasing the next ivory wave.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- Stephens A, Logina I, Liguts V, Aldins P, Eksteina I, Platkajis A, et al. A parkinsonian syndrome in methcathinone users and the role of manganese. *N Engl J Med* 2008; 358:1009–1017.
- de Bie RM, Gladstone RM, Strafella AP, Ko JH, Lang AE. Manganese-induced parkinsonian associated with methcathinone (ephedrine) abuse. *Arch Neurol* 2007; 64:886–889.
- Emerson TS, Cisek JE. Methcathinone: a Russian designer amphetamine infiltrates the rural Midwest. *Ann Emerg Med* 1993; 22:1897–1903.
- Lusthof KJ, Oosting R, Maes A, Verschraagen M, Dijkstra A, Sprong AGA. A case of extreme agitation and death after the use of mephedrone in the Netherlands. *Forensic Sci Intern* 2011; 206:e93–e95.
- Maskell PD, Paoli GD, Seneviratne C, Pounder DJ. Mephedrone (4-methylmethcathinone)-related deaths. *J Analyt Toxicol* 2011; 35:188–191.
- Regan L, Mitchelson M, Macdonald C. Mephedrone toxicity in a Scottish emergency department. *Emerg Med J* 2010 Dec 23. [Epub ahead of print] doi: 10.1136/emj.2010.103093.
- Durham M. Ivory Wave: the next mephedrone? *Emerg Med J* 2011 Mar 15. [Epub ahead of print] doi: 10.1136/emj.2011.112920.
- Wood DM, Davies S, Greene SL, Button J, Holt DW, Ramsey J, Dargan PI. Case series of individuals with analytically confirmed acute mephedrone toxicity. *Clin Toxicol* 2010; 40:924–927.
- Vardakou I, Pistos C, Spiliopoulou C. Drugs for youth via internet and the example of mephedrone. *Toxicol Lett* (2011) doi: 10.1016/j.toxlet.2010.12.014.
- Dargan PI, Albert S, Wood DW. Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. *QJ Med* 2010; 30 July [Epub ahead of print] doi: 10.1039/qjmed/hcq134.
- McElrath K, O'Neill C. Experiences with mephedrone pre- and post-legislative control: perceptions of safety and sources of supply. *Int J Drug Policy* 2011; 22:120–127.
- Brandt SD, Sumnall HR, Measham F, Cole J. Analyses of second generation "legal highs" in the UK: initial findings. *Drug Test Anal* 2010; 2:377–382.
- Karlia L, Reynaud M. GHB and synthetic cathinones: clinical effects and potential consequences. *Drug Test Anal* (2010) doi: 10.1002/dta.210.
- Bronstein AC, Spyker DA, Cantilena LR Jr., Green JL, Rumack BH, Giffin SL. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol* 2010; 48:979–1178.
- Cozzi NV, Sievert MK, Shulgin AT, Jacob III P, Ruoho AE. Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. *Eur J Pharmacol* 1999; 381:63–69.

16. Nagai F, Nonaka R, Satoh K, Kamimura H. The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. *Eur J Pharmacol* 2007; 559:132–137.
17. Fuma T, Kodama T, Honda Y, Tanaka T, Kubo Y, Ohashi N, et al. Influence of methylenedioxypropylvalerone on central nervous system using microdialysis method. *ChemBio Integrated Management* 2009; 5:62–72.
18. Durham M. Ivory wave: the next mephedrone? *Emerg Med J* 2011; doi 10.1136/emj.2011.112920.
19. Archer RP. Fluoromethcathinone, a new substance of abuse. *Forens Sci Int* 2009; 185:10–20.
20. Wood DM, Davies S, Puchnarewicz M, Button J, Archer R, Ovaska H, et al. Recreational use of mephedrone (4-methylenemethcathinone, 4-MMC) with associated sympatomimetic toxicity. *J Med Toxicol* 2010; 6:327–330.
21. Ojanpera IA, Heikman PK, Rasanen JJ. Urine analysis of 3,4-methylenedioxypropylvalerone in opioid-dependent patients by gas chromatography-mass spectrometry. *Ther Drug Monit* 2011; 33:257–263.
22. Kita T, Miyazaki J, Asanuma M, Takeshima M, Wagner GC. Dopamine-induced behavioral changes and oxidative stress in methamphetamine-induced neurotoxicity. *Int Rev Neurobiol* 2009; 88:43–64.
23. Greene SL, Kerr F, Braitberg G. Review article: amphetamines and related drugs of abuse. *Emerg Med Australas* 2008; 20:391–402.
24. Wohlfarth A, Weinmann W. Bioanalysis of new designer drugs. *Bioanalysis* 2010; 2:965–979.