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Inside this issue:

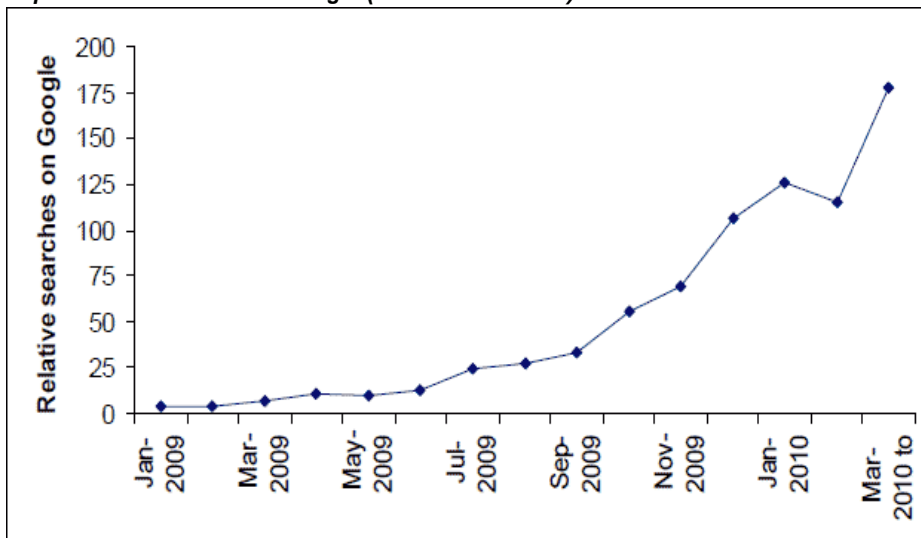
Mephedrone and MDPV: Cathinone Derivatives, Plant Food, Bath Salts or Dangerous Stimulants?	1
Article Submission Requirements and Protocols	15

MEPHEDRONE AND MDPV: CATHINONE DERIVATIVES PLANT FOOD, BATH SALTS OR DANGEROUS STIMULANTS?

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The abuse of Mephedrone, one of the original and best known in a class of designer stimulant drugs marketed as “plant food” and “bath salts”, gained popularity in Europe between 2007–2009, where it rapidly escalated to the United Kingdom’s fourth most popular illegal drug of abuse (following marijuana, cocaine and ecstasy). Its use in the United States was first reported in 2008, where it has paralleled the European experience with an exponential rise in use.^{1,2}

Mephedrone Searches on Google (1/2009 – 3/2010)³



The U.S. is presently lagging behind Europe in legislation and related forensic analysis of Mephedrone and its associated class of cathinone derivative drugs. However, significant efforts are underway to enact laws banning the use, possession and sale of these drugs. Additionally, methods for the forensic analysis of these solid dose drugs as well as for these drugs and related metabolites in blood and urine samples (from individuals suspected to be under their influence), are progressing rapidly.⁶⁻⁹

What is Mephedrone? Mephedrone is also known as 4-methylmethcathinone, 4-methylephedrone or 4-MMC and is the best characterized and studied compound of the drug class known as cathinone derivatives. Cathinone compounds were originally derived from the Khat plant (*Catha edulis*) of eastern Africa and were first synthesized in 1929 and later reintroduced around

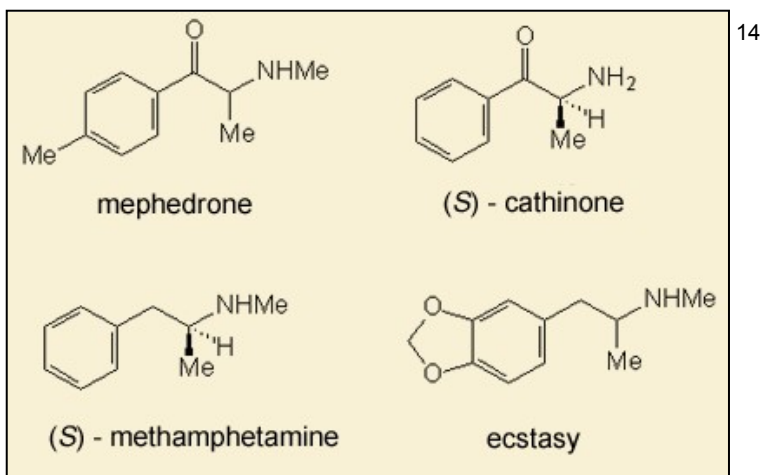
2003. Many U.S. State Controlled Substances Acts are in the process of being updated to include these cathinone derivatives as Controlled Substances, making their use, possession and sale illegal. Of particular interest, are cathinone derivatives with identified medical/therapeutic value, such as Bupropion (Zyban®), a prescription antidepressant and smoking cessation aid, which is typically excluded from these lists.⁸

Mephedrone is often referred to as a “legal high”, because it is not uniformly included in U.S. Federal or State Controlled Substances Acts, is overtly sold as “plant food” or “bath salts” and is labeled “Not for human consumption”. Remarkably, this simple package warning has allowed manufacturers to evade current Federal drug control laws and related prosecution in cases involving cathinone derivatives.^{2,10,11}

Mephedrone is readily available on the web and at local head shops for as low as \$20 per gram. It goes by numerous slang names, including “Meow Meow”, “MCAT”, “4MMC”, “Drone”, “Bubbles”, “Bounce”, “Plant Food”, “Meph”, “Shake n Vac”, “Mad Cow” and others. A standard dose of Mephedrone is reported as 75-200 mg. Mephedrone is typically sold as a fine, white powder that can be insufflated/snorted (most common route of administration), mixed with water and swallowed – often after wrapping in tissue paper (known as bombing or dabbing), inserted rectally as a suppository, or more rarely, injected. Insufflation is frequently performed by “keying”, where a familiar metal key is used as a vehicle to snort the powder; approximately 5-8 keys per gram is typical.^{2,12,13}

Mephedrone vs. Methamphetamine and MDMA (Ecstasy):

Mephedrone is structurally similar to methamphetamine and MDMA.²



Mephedrone Pharmacodynamics/Effects: Mephedrone and the other non-medically useful cathinone derivatives are centrally acting synthetic stimulants that are considered harmful and dangerous drugs, with effects similar to amphetamine, to which they are closely related. They are also often compared to and marketed as “good alternatives” to MDMA (Ecstasy), cocaine, methamphetamine and other euphoric stimulants. Mephedrone is also considered to have significant empathogenic or empathy generating effects, again comparable to the structurally similar drug, Ecstasy.^{2,15,16}

Mephedrone’s short duration of effects along with its intense initial rush are primary causes of numerous reports of compulsive re-dosing by users. This is also the source of significantly greater use

of the drug than intended, which is consistent with the rash of recently reported mephedrone-related ER overdose visits. The cathinone derivatives can cause anxiety and paranoid states; over-stimulation of the cardiovascular system, with risk of heart and circulatory problems; over-stimulation of the central nervous system, with risk of seizures, extreme agitation, paranoia, hallucinations; and a significant risk of drug dependency.^{17,18}

Death risk associated with stimulants usually involves cardiovascular problems, overheating and dangerous drug interactions as well as accidents related to intoxication and multi-drug combinations (often, both dose & polypharmacy related).^{19,20}

Mephedrone Summary of Effects:²¹

Positive Effects	Neutral / Negative Effects
Mental / physical stimulation (body energy) Euphoria, mood lift Feelings of empathy, openness Increase in sociability, desire to talk with others Pleasurable rushing - sense of being pleasantly sped up	Decreased appetite Pupil dilation / mydriasis Increased heart rate and blood pressure Compulsive re-dosing, craving to recapture initial euphoric rush Uncomfortable changes in body temperature (sweating / chills) Heart palpitations, sense of racing heart Impaired short term memory Insomnia Tightened jaw muscles, clenching / grinding of teeth Muscle twitching Nystagmus (?) Dizziness, light headedness, headache and vertigo Few reports of vasoconstriction w/re-dosing, including moderate to severe symptoms of tingling and numbness in extremities and skin discoloration



22

The onset of effects, with insufflation, is usually felt within a few minutes and peak effects within 30 minutes. With oral administration, effects are dependent upon recent food intake. Both the amount of food ingested and how recently it was consumed will affect drug absorption and onset of effects. Typically, 15-45 minutes are required for the drug's full effects to be achieved; this time will be increased with the presence of significant food in the gut. With oral administration, primary drug ef-

ffects last approximately 2-3 hours. After 1-4 hours, many individuals find it difficult to sleep, although mood and mind-set are generally back to normal. As previously noted, strong re-dose urges are commonly reported while effects wane (45-120 minutes post dosing). Under high dose conditions, worrying, neurological and vasoconstrictive side effects are common and are reported to last for days or even weeks.^{2,21,23}

Research at the University of Sunderland, lead by Dr. John Lough in 2010, showed significant variance in the quality of mephedrone samples purchased over the Internet and related impact of quality differences on the risk of overdose. Various particle sizes and crystalline forms were found in purchased mephedrone samples. Research indicated that the different particle sizes and crystalline forms of mephedrone were likely to provide variations in how individuals were affected upon use of the drug.²⁴

Mephedrone: Oral Duration of Effects ²¹

Total Duration	2 - 5 hrs
Onset	15 - 45 mins
Coming Up	15 - 30 mins
Plateau	15 - 30 mins
Coming Down	30 - 90 mins
After Effects	2 - 4 hrs
Hangover / Day After	Days / weeks



What is MDPV?

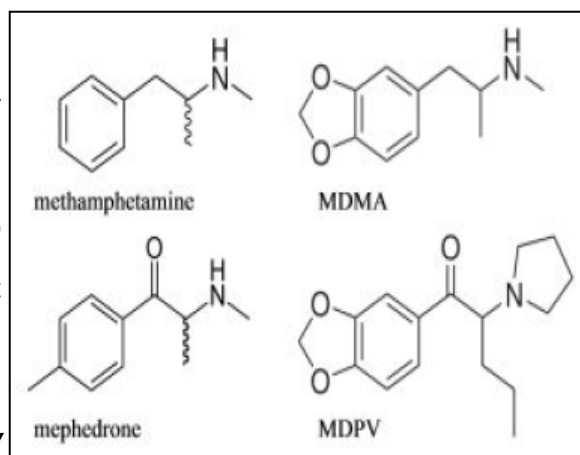
MDPV, also known as Methylenedioxypropylvalerone, is also included in the cathinone derivative class of designer stimulant drugs. MDPV was first synthesized as part of a class of stimulants in 1969 and is the methylenedioxy analogue of pyrovalerone, a Schedule V stimulant first synthesized in 1964. Pyrovalerone, available under the trade names Centroton® and Thymergix®, is used in Europe as an appetite suppressant or for the treatment of chronic fatigue. MDPV is chemically related to both methylphenidate (Ritalin®), Pyrovalerone (PV), and also to methylenedioxymethamphetamine or MDMA (Ecstasy). MDPV is currently unscheduled in the United States, is found as a white or light tan powder, and is reported to develop a distinctive odor when exposed to air.^{2,26,27}

Pharmacodynamics / Effects of MDPV:

MDPV is a powerful stimulant with stimulatory effects on the central nervous system and cardiovascular system. While structurally similar to Methylphenidate/Ritalin®, it is reported to have four times its potency.^{2,28} MDPV is frequently advertised online as legal cocaine or legal amphetamine.

MDPV effects include: rapid heartbeat, increased blood pressure, vasoconstriction, sweating, euphoria, increased alertness and awareness, increased wakefulness and arousal, anxiety, agitation, perceived appetite suppression and

diminished need for sleep. MDPV is commonly described as boosting a user's libido; however, it is also associated with extreme anxiety at higher dosages. Duration of effects are roughly 3 to 4 hours, with after effects such as tachycardia, hypertension and mild stimulation lasting from 6 to 8 hours. High doses have been reported to cause intense, prolonged panic attacks in non-tolerant users. There are also anecdotal reports of psychosis from sleep withdrawal and addiction at higher doses and/or more frequent dosing intervals. MDPV has been described by both professionals and users, as "strongly addicting".^{28,30}



"Bath Salts" and the recent emergence of MDPV in the U.S.

29

Both Mephedrone and MDPV are stimulant compounds found in "Bath Salt" preparations. Because of the emerging nature of these drugs, most specifically MDPV to the U.S. marketplace, there seems to be confusion regarding MDPV and what other drugs such as Mephedrone, are being used in "Bath Salt" preparations.

MDPV Timeline:³¹

- 1960s:** Developed and used for the treatment of chronic fatigue (caused problems of abuse and dependence).
- 1969:** Boehringer Ingelheim files a patent application for MDPV.
- 2005:** Appears as a recreational drug; first mention on Drugs-Forum.
- 2007:** First seizure as a recreational drug (by customs officials in Germany; the drug had been shipped from China).
- 2008:** First seizure in the U.S.
- 2009:** Made illegal in Denmark.
- 2010:** Made a controlled drug in the UK and Sweden. First reports of widespread retail marketing of "bath salts" containing MDPV in the US (currently, also illegal in Germany, Australia and Finland).
- 2011:** Sale and possession banned in the U.S. states of Florida and Louisiana.

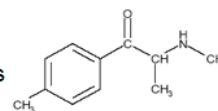
A U.S. Dept of Justice report from December 2010 states that "preliminary testing indicates that the active ingredients in many brands [of bath salts] contain MDPV and/or mephedrone."³² Again, because of the emergent nature of this class of substances, there has been some question as to what is in the composition of "Bath Salts". Most evidence now supports MDPV as the *current* compound of choice for "Bath Salts".³³

An alarming number of anecdotal stories involving "Bath Salt" usage and their potential for harm have come from national and local news stories, online reports, local emergency room reports and data collected from the American Association of Poison Control Center. In 2010 there were 302 calls regarding MDPV ("Bath Salt" products) according to the American Association of Poison Control Centers' National Poison Data System.

Evolution of Synthetic Stimulant Constituents in "Bath Salts": 2,34,35

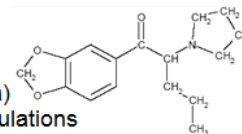
1) Mephedrone (aka: 4-Methylmethcathinone; 4-MMC)

- Most frequently encountered cathinone derivative, similar to the amphetamines
- Common synthetic stimulant in first generation "Bath Salts" (2008-2009 era)
- Banned in UK in August 2010 as Class B Drug



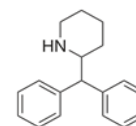
2) MDPV (aka: Methylenedioxypropylvalerone)

- Cathinone derivative similar to Methylphenidate (Ritalin®) and Pyrovalerone
- Common synthetic stimulant in second generation "Bath Salts" (2009-2010 era)
Currently most frequent ingredient found in U.S. "Ivory Wave, Bath Salts" formulations
- Banned in UK in August 2010 as Class B Drug



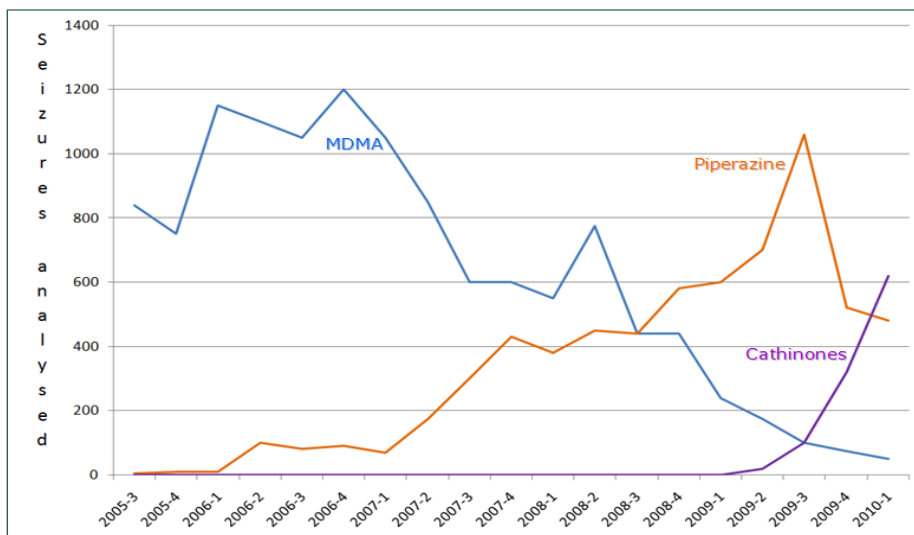
3) Desoxypipradrol (aka: Deoxypipradrol; 2-(diphenylmethyl) piperidine; 2-DPMP)

- *Not* a Cathinone derivative, but a piperidine
- Structurally similar to methylphenidate (Ritalin®), prescribed for ADHD
- Synthetic stimulant in third generation "Bath Salts" (2010-2011 era)
In response to Aug 2010 ban of mephedrone and MDPV as Class B Drugs
- UK banned importation in Nov 2010; considering ban as Class B Drug
- As of March 2011, still a "Legal High" in UK and U.S.



As of March 23, 2011 U.S. Poison Control Centers reported 1,511 calls regarding MDPV, approximately five times as many calls in the first 3 months of 2011 than for all of 2010.³²

The National Institute of Drug Abuse (NIDA) has made a public statement concerning MDPV on their website, characterizing it as a dangerous chemical. However, as of March 1, 2011, the U.S. Federal Government has yet to enact legislation against MDPV.³⁷



The number of samples analyzed by the UK's Forensic Science Service of seized MDMA (Ecstasy), piperazines (BZP, a popular club drug similar to Ecstasy) & cathinones (Mephedrone and MDPV) between the third quarter of 2005 and the first quarter of 2010 (London, UK July 2010).³⁸



36

Mechanism of Action: The mechanism of action of Mephedrone and the cathinone derivatives is essentially unknown. It is considered likely to involve both the Dopamine and Serotonin neurotransmitters. As virtually *all* drugs with related addiction increase Dopamine release in the mesolimbic pathway of the brain, this is consistent with the proposed mechanism of action.^{2,39} MDPV is thought to function as a Dopamine-Norepinephrine reuptake inhibitor.⁴⁰



By way of example, compare the fairly well understood mechanism of action of Cocaine. The three principal neurotransmitters involved in producing the stimulating effects of Cocaine are:

- 1) Cocaine primarily blocks Dopamine reuptake transporter, which produces euphoria, psychosis and altered perceptions. 41
- 2) Norepinephrine - increases alerting, stimulating and locomotor effects.
- 3) Serotonin (5-HT) - increases energy, sociability, delusions and psychosis.⁴²

Contraindications & Drug-Drug Interactions:

Mephedrone or MDPV should not be combined with Monoamine Oxidase Inhibitors. MAOIs are commonly found in prescription anti-depressants, including Phenzelzine / Nardil® and others. Any stimulant plus a MAOI is a potentially dangerous combination. Individuals with seizures, convulsive disorders or heart problems, are generally at greater risk for resulting health problems when taking stimulants.² Reports of Mephedrone users combining the drug with alcohol, cannabis and other stimulant illicit drugs are common, actually this described polypharmacy appears far more common than for single drug use of Mephedrone. The combination of Mephedrone with other illicit, prescription drugs and/or alcohol may produce additive, possibly synergistic (the sum being greater than the contribution of the two drugs alone) effects. Some polypharmacy combinations can produce severe effects, including marked reductions in human performance, all the way to death or near death physiological consequences.¹⁹

Mephedrone / MDPV Impaired Driving:

Do not operate heavy machinery or drive when taking Mephedrone or MDPV. As is well documented with any stimulant abuse, any short term “benefits” of perceived heightened energy and awareness are far outweighed by the concomitant loss of divided attention, increased risk taking, etc. that are critical to the safe operation of a motor vehicle.⁴³ Videos of reported Mephedrone-impaired individuals, along with some Mephedrone-impaired drivers, are available online.⁴⁴ The vast majority of individuals seen, do not appear to be viable candidates for safe driving.

Case Studies:**1) UK, Mephedrone Fatality (internet report) ⁴⁵**

Recently married, Sarah Forsyth, a 35 year-old woman, died after falling into a coma, ten months after she read online that “Ivory Wave” could help with weight loss. Her parents said she dropped from a size 16 to a size 6 after taking the drug for just four months, and became paranoid and aggressive. Forsyth then fell into a coma and eventually died of brain edema and heart failure.

2) UK, Mephedrone ER presentation and discharge (journal publication 4/1/10) ⁴⁶

A 22-year-old man purchased 4 g of mephedrone powder over the Internet from a chemical supplier based in China. He initially ingested 200 mg of the mephedrone orally, with no perceived clinical effects, and thereafter after a “few hours,” injected the remaining 3.8 g intramuscularly into multiple sites on both his thighs. Shortly after the injection, he developed palpitations, “blurred tunnel vision,” chest pressure, and sweating and felt generally unwell; he presented to hospital with continuing features of sympathomimetic toxicity. His symptoms settled over the next 4 h after a single dose of oral Lorazepam. Qualitative analysis of the urine and serum sample was undertaken using gas chromatography with mass spectrometric (GC/MS) detection, both positive for the presence of 4-methylmethcathinone. Quantitative analysis of the serum sample was undertaken by liquid chromatography with tandem mass spectrometric detection; the estimated mephedrone concentration was 0.15 mg/l. Routine toxicological analysis of the serum and urine specimens using a broad GC/MS toxicology screen did not detect any other drugs or alcohol.

He was reviewed by the clinical toxicology service on presentation to the ER with the following signs and symptoms:

anxious and agitated

elevated heart rate of 105 beats per minute

elevated blood pressure of 177/111 mmHg

dilated pupils of 7 mm

normal body temperature of 36.2°C

respiratory rate of 18 breaths per minute

remainder of his neurological examination was normal

no evidence of hypertonia or hyperreflexia

no inducible/spontaneous clonus (jaw clenching) or bruxism (teeth grinding)

visual field examination normal

admission electrocardiogram showed a sinus tachycardia

normal lab work: potassium, creatinine, glucose and venous blood gas

In view of agitation and other ongoing sympathomimetic features, treated with 1 mg Lorazepam orally and admitted for observation

Over next 4 hr, agitation and anxiety settled, along with clinical indicators of sympathomi-

metic toxicity (heart rate of 90 bpm and blood pressure of 110/67 mmHg)

Discharged following 6 hr treatment/observation in ER

Toxicological analysis of serum and urine samples collected on admission, when patient was clinically symptomatic, was performed. Qualitative analysis of the urine and serum sample was conducted using gas chromatography/mass spectrometry (GC/MS) detection. Urine and serum samples were both positive for the presence of 4-methylmethcathinone (mephedrone). Quantitative analysis of the serum sample was conducted by liquid chromatography with tandem mass spectrometry detection. The serum concentration of mephedrone was estimated to be 0.15 mg. This is the first reported case of isolated Mephedrone toxicity, with confirmatory analytical findings.

3) Kansas, 2010 MDPV fatality (internet report)⁴⁷

21-year-old Kansas University student, Elijah Taylor, ran waving his hands onto Interstate 135 and directly into the path of an oncoming van which struck and killed him. Police discovered a container of Blue Magic "Bath Salts" in his pocket. Toxicology tests confirmed the presence of the synthetic stimulant MDPV at autopsy.

Police investigations also revealed that Taylor had been a passenger earlier in a vehicle on Interstate 135, when he exhibited aggressive and bizarre behaviors. He battered the driver and started kicking the windshield. Taylor was removed from the vehicle and left at the side of the Interstate, where he then ran into the path of the van and was struck. Taylor had been with a friend earlier in the evening and had been reportedly smoking a street drug marketed as "potpourri" and also had in his possession a small blue container of "bath salts."

4) Missouri, Oct 2010 MDPV suicide (internet report)⁴⁸

29-year-old Jarrod Moody of St. Joseph committed suicide, allegedly after a binge on Ivory Wave "Bath Salts". Moody had reportedly been off painkillers for two years when he developed an addiction to Ivory Wave. His father said he had found several packets of the bath salts in his son's room. Moody's friends and family described him as emaciated, paranoid and sleepless in the days leading to his death. He had just made it through a dark spell in life, beating a prescription drug addiction and securing a steady job.

But sometime in September, friends and family noticed a change in Jarrod. "He wasn't eating, was going from being totally off the wall and not feeling well to being way over the top," John Moody said. After his suicide, Jarrod's friends came forth and explained he had recently developed an addiction to the powdery substance. Toxicologists found MDPV in his system at autopsy.

Legal Aspects:

Cathinone/Methcathinone derivatives, Mephedrone and MDPV, continue to be marketed/sold as research chemicals and bear prominent package labeling of "Not for human consumption".⁴⁹

Mephedrone / MDPV no longer a "Legal High" – synthetic cathinones currently banned in:^{9,50}

2008 Israel, Denmark and Finland

2009 Sweden, Estonia and Guernsey

2010 Germany, Croatia, Romania, Isle of Man, Netherlands, United Kingdom (April 16, 2010), Ireland, Belgium, Italy, Lithuania, France, Norway, Russia, Austria, Poland, China, Singapore, Australia, Canada and New Zealand.

Now illegal (as of March 31, 2011) in 13 U.S. states: Alabama, Florida, Hawaii, Idaho, Kentucky, Louisiana, Michigan, Mississippi, North Carolina, North Dakota, Utah, Virginia and Wyoming. Additional states are currently considering legislation to make these drugs and related synthetic cathinones scheduled controlled substances.

In February, 2011, Director of the National Drug Control Policy, Gil Kerlikowske, released the following statement regarding MDPV and “bath salts”: he was “deeply concerned,” and “public health officials are working on this emerging issue.”⁵¹ As national public health officials now have MDPV on their radar, many anticipate a national U.S. emergency ban will occur in 2011.

Final Considerations:

The following are appropriate “take home messages” for the cathinone / methcathinone derivatives and related Mephedrone and MDPV drugs. Be on guard for these drugs (prepare law enforcement, forensics and prosecution to deal effectively with enforcement, analysis, testimony, etc. as these drugs have clearly emerged as significant drugs of abuse in the U.S.

The following considerations make the current situation particularly treacherous:

- These drugs are associated with negative/dangerous effects (including toxicity and related deaths), addiction, suicide, etc.
- Significant driving impairment potential is consistent with these drugs.
- Few peer-reviewed publications exist regarding these drugs and their negative effects on humans and their related performance.
- Delayed effective Federal and local legislation, regarding these drugs, is currently at work.
- Many Forensic and other related Labs are not yet testing (adequately screening) for these drugs.⁵²

With the current heightened interest surrounding these drugs, additional quality information can undoubtedly be anticipated.

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