

Cathinone Analogs (AKA “Bath Salts”) and California Regulation



California Conference of Local Health Officers Semi-annual Meeting

October 19, 2011

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(Credit for Pharmacology Slides to Timothy Rohrig, PhD, from the Regional Forensic Science Center,)

Alternate Names For

BATH SALTS

ARCTIC BLAST	COTTON CLOUD	MYSTIC	WHITE GIRLS
BAYOU IVORY FLOWER	DYNAMITE DYNAMITE PLUS	OCEAN SNOW	WHITE HORSE
BLOOM	ENERGIZING AROMATHERAPY POWDER	PURE WHITE	WHITE KNIGHT
BLUE MAGIC	EUPHORIA	RED DOVE	WHITE LIGHTNING
BLUE MAGIC	GOLD RUSH	ROUTE 69	WHITE RUSH
BLUE SILK	HURRICANE CHARLIE	SCARFACE	WICKED X
BOLIVIAN BATH	IVORY FRESH	SNOW DAY	WICKED XX
BONSAI WINTER BOOST	IVORY WAVE	SNOW LEOPARD	ZOOM
C ORIGINAL	IVORY WAVE ULTRA	TRANQUILITY	
CLOUD 10	LADY BUBBLES	VANILLA SKY	
CLOUD 10 ULTRA	LUNAR WAVE	WHITE CHINA	
CLOUD 9	MR. NICE GUY	WHITE DOVE	



Eclipse “Bath Salts:” A Users Diary

- Blog recorded 6/29/2010

“Swims ferret recently got a 1g package of Eclipse exotic [bath salts](#). Swims ferret was sniffing around in the bag and tried 2 very small lines over a 1 hour period (eyeballed 1/20 of bag).

The ferret found himself energized, alert, not really euphoric, but did notice a mild visual distortion. The ferret also stated that although he was alert, he was somewhat confused and had trouble completing anything that takes complex problem solving without getting distracted. The ferret said that effects lasted 4-6 hours and slept well at night.

Perhaps the ferret will try a more decent sized dose tomorrow.”

- Blog recorded two weeks later

“0:00 Ferret insufficated (sic) ~50mgs and orally took another ~75mgs

0:15 Ferret feels somewhat more alert, no real feeling of euphoria

1:00 Ferret still isnt high so orally takes another ~75mgs

1:30 More energy, starting to feel confused, but still not high...”

2:00 Ferret is thinking this product really isn't anywhere near the energy or focus that amphetamines (adderall) produce. Ferret then takes two otc energy pills that he takes every day and alone are not really effective at all, with another ~75mgs.

2:30 Ferret is overcome with the need to move, ferret can feel his heart trying to beat out his chest. Ferret becomes so confused, he cannot focus on anything, vision is blurred, ferret is scared that he took too much.

2:45 Ferret induces vomiting, doesn't come easy. Ferret still cannot sit, ferret is breathing heavily kind of like a panic attack.

3:00 Ferret lies on couch trying to calm himself down

4:00 Ferret is still uncomfortable, but now anxiety has lessened, but still breathing heavily with heart still breaking out of his chest.

5:00 Ferret is starting to calm down, he is still confused and feels his body still revved up, but his mind is shot.

6:00 Ferret can finally walk around and accomplish things again. Ferret goes and takes his blood pressure and it is 180 / 120 (normally 120/80) rested. Ferret regrets this whole exp.

10:00 Ferret can sleep fine, everything is back to normal.

Sum up: this product alone did little to provide pleasure, mental energy and focus. ...The effects seemed to be purely body stimulation with confusion in the brain. Ferret would not recommend this product.”

Public Health Investigation:

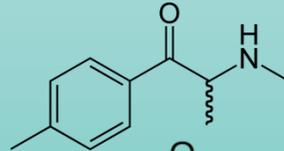
- **May 4, 2011:** A 26-year-old male patient with a prior history of drug use presents to a local Urgent Care Center feeling a “sense of doom,” nervousness, shortness of breath, hallucinations, chest pain and inability to rest. He had recently dissolved and injected “Eclipse Bath Salts” into his antecubital vein. The patient is found to have drug-induced delirium, tachycardia and conduction abnormalities of the heart suggestive of cardiomyopathy.
- **May 5 and 6, 2011:** The patient undergoes stress tests, monitoring and counseling as an inpatient. Follow-up is scheduled at the time of discharge with cardiologist and Behavioral Health.
- **May 13, 2011:** “Eclipse Bath Salts are found for sale at a local “Head Shop.” The store owner refuses to remove this product and other “Bath Salts” from his shelves because it “is not illegal.” He is informed by the Health Officer that MDPV is illegal and is in the Bath Salts he is selling.
- **July 4, 2011:** The patient is found dead near a local homeless camp. Cause of death listed as acute subdural hematoma.

Ingredients in Products Sold as “Bath Salts”

- Synthetic Cathinone analog drugs

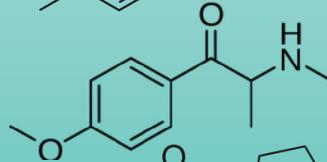
Most Common:

Mephedrone



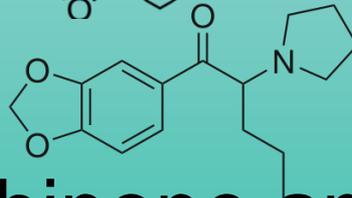
(4-methylmethcathinone)

Methedrone



(4-methoxymethcathinone)

MDPV



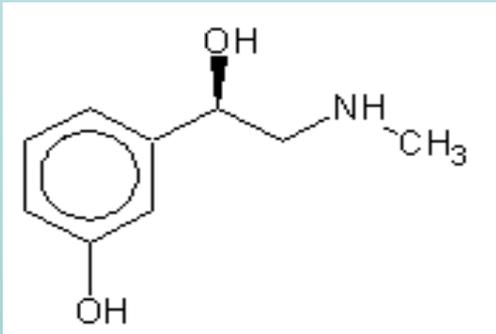
(methylenedioxypropylvalerone)

Many Other Cathinone analogs

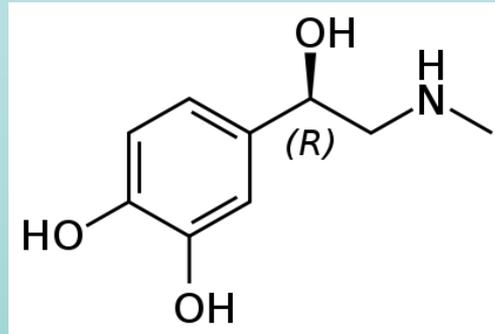
Flouromethcathinones

Mixtures of several analogs

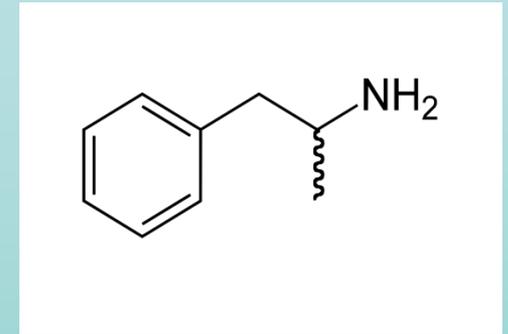
Adrenergic Agents



Phenylephrine

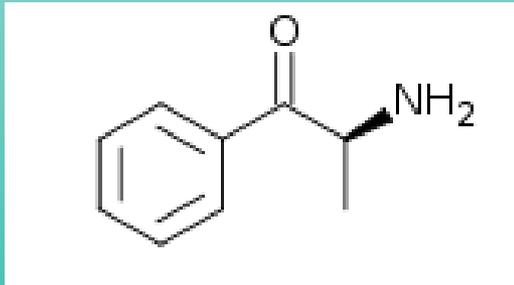


Epinephrine

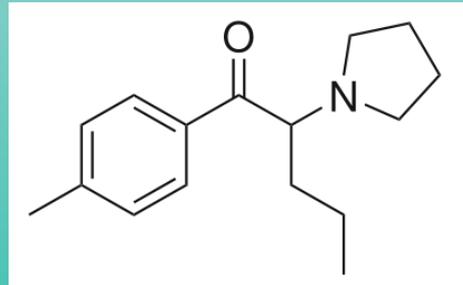


Amphetamine

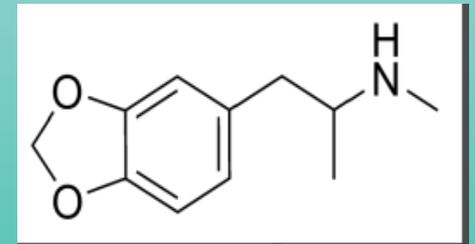
Cathinone Analogs



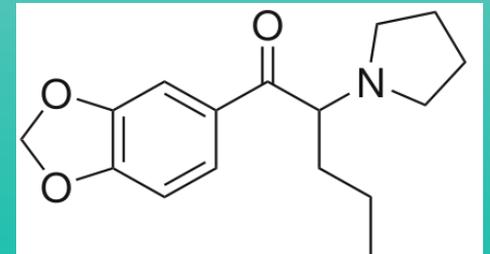
Cathinone, AKA
2-amino-1-phenyl-1-propanone



Pyrovalerone



MDMA, AKA "Ecstasy"



MDPV

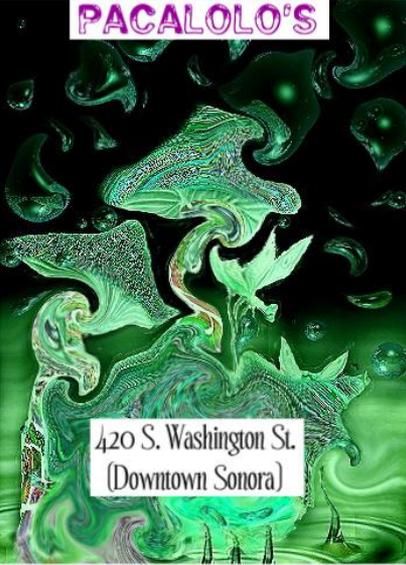
Products are most often purchased online or at various “Head Shops” as “Bath Salts” or “Plant Food.”



K2 INCENSE ONLINE
THE ALTERNATIVE PHARMACY - OFFICIAL AND AUTHENTICATED



PACALOLO'S



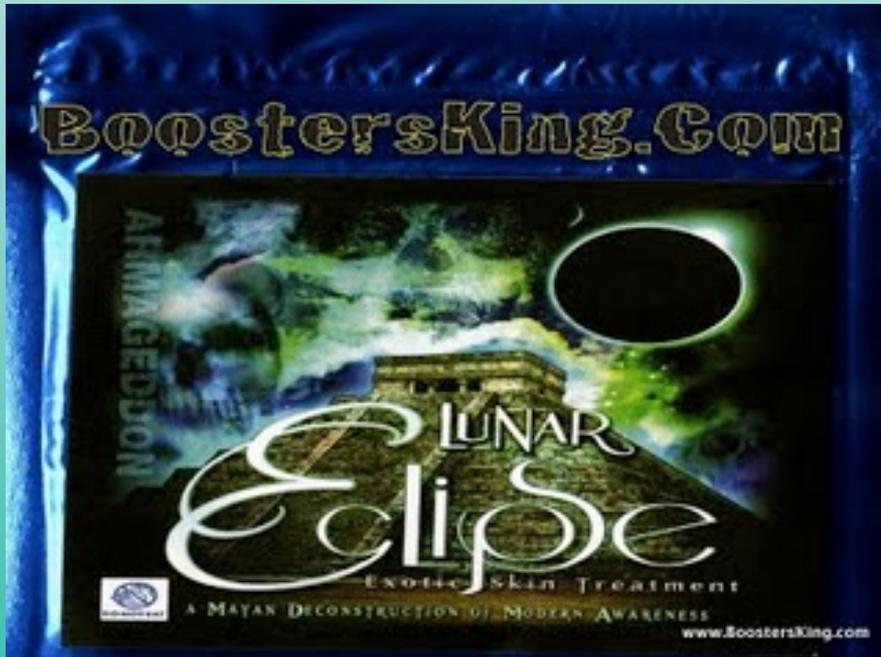
420 S. Washington St.
(Downtown Sonora)

www.myspace.com/sonorapacalolo

The dangerous products are not easily confused with legitimate Bath Salt products...at least by health-conscious people



The dangerous products are not easily confused with legitimate Bath Salt products...at least by health-conscious people



↑
“A Mayan Deconstruction of Modern Awareness”

The dangerous products are not easily confused with legitimate Bath Salt products...at least by health-conscious people



Research was done on cathinone analogs in the 1960s

- **Acute poisoning involving the pyrrolidinophenone-type designer drug 4'-methyl-alpha-pyrrolidinohexanophenone (MPHP).**

Sauer. C, Hoffmann K, Schimmel U., Peters FT Institute of Forensic Medicine, University Hospital Jena, D-07740 Jena, Germany 2011

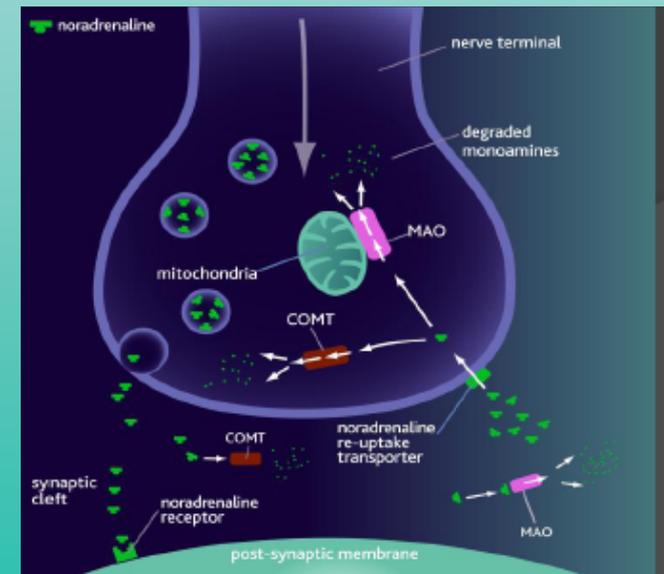
- **1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogs. A promising class of monoamine uptake inhibitors**

Peter C. Meltzer,†* David Butler,† Jeffrey R. Deschamps,†† and Bertha K. Madras†††, J Med Chem. 2006 February 23; 49(4): 1420–1432.

“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.”

General Pharmacology of Cathinone Derivatives

- **Cathinones behave as central nervous system stimulants, acting through direct binding to adrenergic receptors and by promoting the release of other monoamines and inhibition of reuptake**
 - ✓ dopamine
 - ✓ serotonin
 - ✓ norepinephrine
- **Studies of effects of cathinones on monoamine neurotransmission in rat brain confirm mechanisms of action similar to amphetamines**



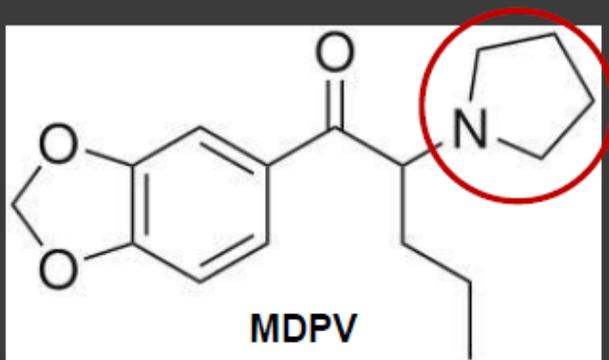
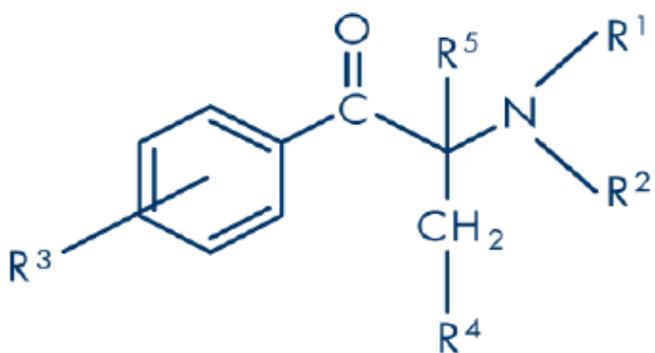
General Pharmacology of Cathinone Derivatives

- **Cathinones generally display lower potency than phenylethylamine analogs due to the β -keto group creating a more polar molecule which is less able to cross the blood brain barrier**
 - ✓ The pyrrolidine ring and tertiary amine in MDPV renders it more lipophilic and therefore more able to cross into the CNS



- **The direct catecholnergic effect results in activation of adenylyl cyclase, converting ATP to cyclic AMP. A synergistic effect occurs with phosphodiesterase inhibitors, like methylxanthines, accentuating the stimulant effect**

General Structure of Cathinone Derivatives



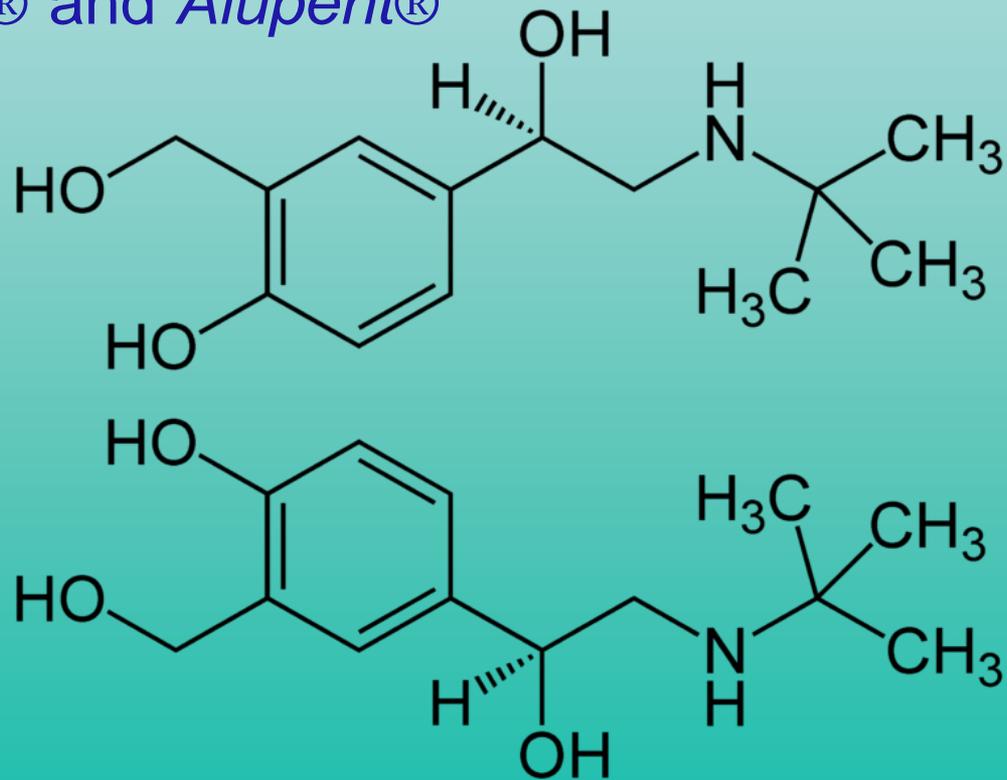
R ¹	R ²	R ³	R ⁴	R ⁵	Name
H	H	H	H	H	Cathinone
Methyl	H	H	H	H	Methcathinone (ephedrone)
Methyl	H	4-Methyl	H	H	Mephedrone (4-MMC; M-CAT)
Ethyl	Ethyl	H	H	H	Diethylpropion* (Amfepramone)
t-Butyl	H	3-Cl	H	H	Bupropion*
Methyl	H	3,4-Methylenedioxy	H	H	Methylone (βk-MDMA)
Methyl	H	4-Methoxy	H	H	Methedrone (βk-PMMA)
Methyl	H	3-F	H	H	3-Fluoromethcathinone (3-FMC)
Pyrrolido		4-Methyl	Ethyl	H	Pyrovalerone
Pyrrolido		3,4-Methylenedioxy	Ethyl	H	3,4-Methylenedioxy-pyrovalerone (MDPV)

* Therapeutics

βk = beta keto
PMMA – paramethoxymethamphetamine

Minor modifications or selective isolation of drug enantiomers has been used by the pharmaceutical industry for decades as a way to sustain drug patent protection

- *Nexium*® and *Prilosec*®
- *Xopenex*® and *Alupent*®



General Pharmacology

- Effects are claimed to be similar to those of cocaine, amphetamine or MDMA
 - Suspected mephedrone intoxication
 - Sympathomimetic effects to similar to amphetamine derivatives
- Few formal studies on the pharmacokinetics or pharmacodynamics



General Pharmacology

Action of Selected Drugs on Monoamine Transporters *

	Dopamine	Serotonin	Noradrenaline
Amphetamine	+++	+	++++
MDMA	++	+++	+++
Cathinone	+++	++	+++
Methcathinone	+++	+	+++
Methylone	++	+++	++++
Mephedrone	?	?	?



* Relative affinities since studies did not use same units

+ low affinity ++++ high affinity

***Cathinones were potent inhibitors of the noradrenaline transporter [NET]
- strong sympathomimetic action***

Cozzi et al (1999) Eur J Pharmacol 381:63

Nagai et al (2007) Eur J Pharmacol 559:132

Pharmacology – Mephedrone [4-MMC]

- Common Hospital presentations
 - Tachycardia and palpitations
 - Hypertension
 - Dilated pupils
 - Agitation
 - Seizure
 - Nausea and vomiting
 - Headache
 - Hx of bruxism
 - Insomnia
 - Hallucinations and psychosis @ high dosing



Mephedrone Fatality

- Lusthof et al (2011) describes a case of extreme agitation and death after the ingestion of mephedrone [4-MMC]
 - 36 yr old male arrested by police after being injured from smashing windows in a “rage of fury”
 - Died shortly thereafter despite resuscitation attempts
 - Autopsy showed superficial skin lacerations, bruises and minor brain swelling
 - Tox: FB **4-MMC - 5.1 mg/L**
 - Trace: cocaine, MDMA and oxazepam
 - COD: excited delirium due to mephedrone intox
 - Contributing condition: blood loss - multiple wounds



MDPV Pharmacology

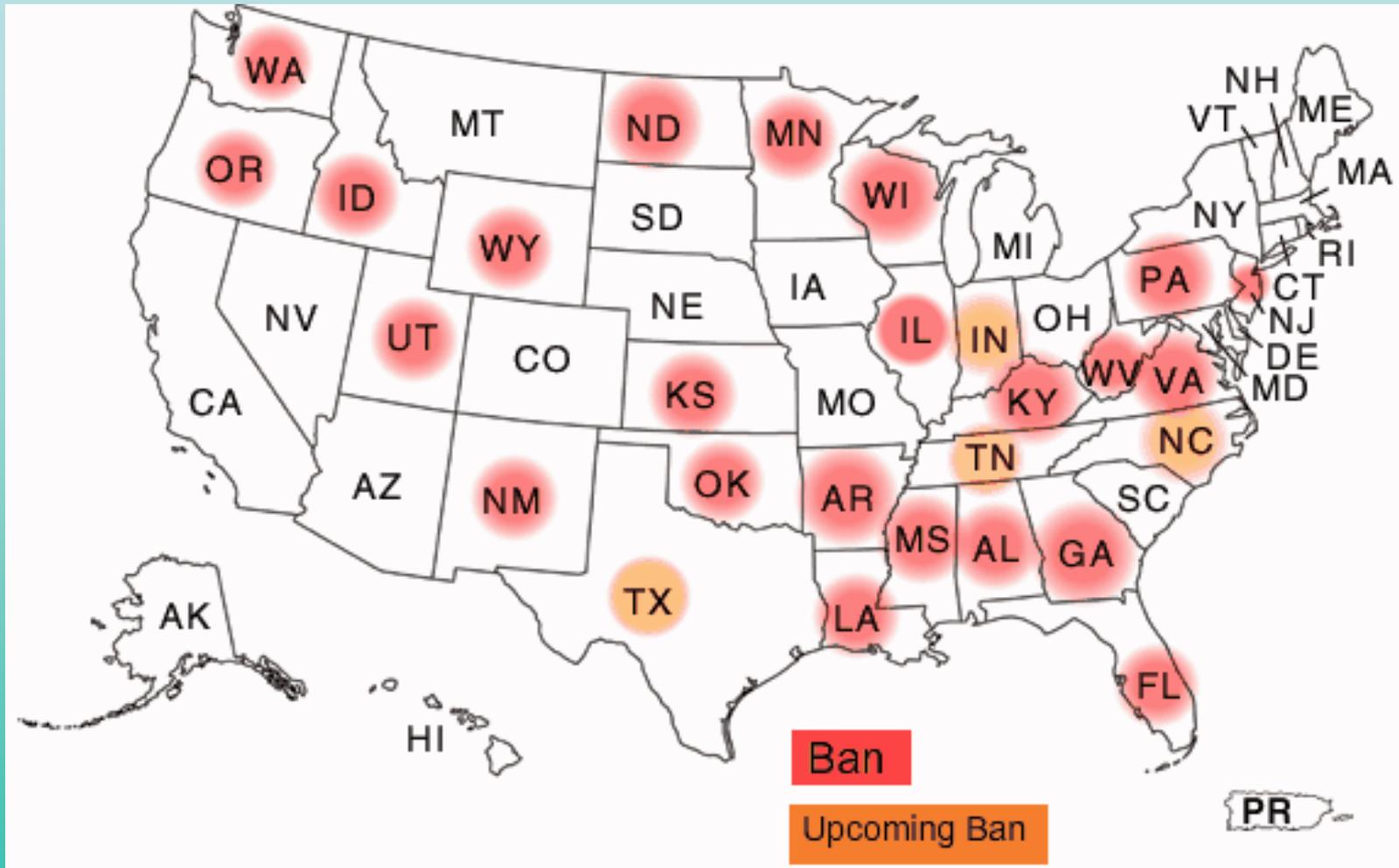
- MDPV is a ring substituted analog of pyrovalerone
- The drug was developed in the 1960s and was studied for any possible therapeutic value:
 - ...for treatment of chronic fatigue
 - ...as an anorectic agent
 - ...noted to pose risk of abuse and dependency
- Found to have four-fold higher potency than methylphenidate
- Pyrovalerone had problems with abuse and dependence

Distribution of MDPV

Specimen	Concentration
Blood [Hospital: 12/21/10 @ 0050 hrs]	0.04 mg/L
Serum [Hospital: 12/21/10 @ 0050 hrs]	Positive (<0.04mg/L)
Heart Blood	0.03 mg/L
Femoral Blood	0.02 mg/L
Vitreous	Positive (<0.03 mg/l)
Liver	0.09 mg/kg
Brain	0.08 mg/kg
Urine	Positive

Death Pronounced at 0022 hrs on 12/22/10

States Banning "Bath Salts"



For the sake of this review, "bath salts" are defined as follows:
*Mephedrone//MDPV//3-FMC//4-FMC ("flephedrone")//BK-PMMA ("methedrone")//methylone//butylone.

CA Health and Safety Code 11400

...it is the intent of the Legislature that a controlled substance analog as defined in Section 11401 be considered identical, for purposes of the penalties and punishment specified in Chapter 6 (commencing with Section 11350), to the controlled substance in Section 11054 or 11055 of which it is an analog.”

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The DEA classifies Cathinone as a “non-narcotic” Schedule 1 drug

Schedule I			
Substance	DEA Number	Non Narcotic	Other Names

Betaprodine	9611		
Bufotenine	7433	N	Mappine, N,N-dimethylserotonin
Cathinone	1235	N	Constituent of "Khat" plant
Clonitazene	9612		
Codeine methylbromide	9070		
Codeine-N-oxide	9053		
Cyprenorphine	9054		

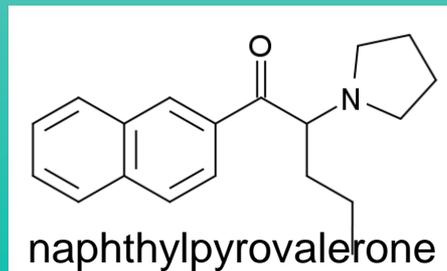
The Analog Drug Law, Health and Safety Code Section 11400, provides that selling a drug that is an analog of a scheduled controlled substance is a crime, and can be prosecuted as a felony.



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Because sellers of cathinone derivatives were not being prosecuted under H&S 11400, AB 486 (Hueso) was passed through both houses in the 2011-12 California legislative session and signed by the governor on 10/9/2011, making...

“...it a crime, punishable by imprisonment in a county jail not exceeding 6 months, or by a fine not exceeding \$1,000, or by both that fine and imprisonment, to sell, dispense, distribute, furnish, administer, or give, to offer to sell, dispense, distribute, furnish, administer, or give, or to possess for sale, any synthetic stimulant compound or any specified synthetic stimulant derivative, including naphthylpyrovalerone and 2-amino-1-phenyl-1-propanone...”



Strategies to consider...

- Identify in your county the retail locations where these products are being sold
- Inform the merchants that the products being sold are illegal if they contain cathinone derivatives
- Speak to your District Attorney about prosecuting establishments that continue to sell these products
- There is clear regulation now making the sales of cathinone derivatives and other stimulants illegal
- Ask your DA to consider prosecuting under Health and Safety Code 11400 to maximize penalties when appropriate.