

## Psychoactive Substances in Convenience Store Clothing: The Recent Trend of Synthetic Cannabinoids (K2/Incense) and Cathinones (Bath Salts) as “Legal Highs”



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"It was the best of times, it was the worst of times" – Charles Dickens

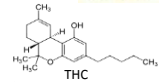


- Heaven and Hell
- Wolf in Sheep's Clothing...
- Better than Weed!
- First Time - Very Impressed
- It was a terrifying. Blissful trip.
- Violently Puking and Delirious Hallucinations
- Terrifying, Will Never Touch It Again
- High on a Wave on a Dream
- The Night I Killed My Friends
- From mildly pleasant to fear of death
- First Time - A fantastic cannabinoid
- Blonde (vaporized) made me feel a full-on weed high
- Brain melting pain just isn't worth it
- The fear, visuals, and tremors continued
- The battle between good and evil in my head

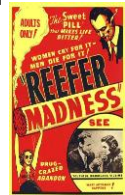
## “Legal Highs” Coming to America



## A Very Incomplete History of Cannabinoids

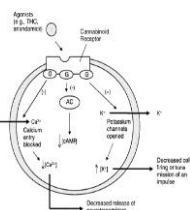


- Cannabis medical and recreational use dates back to B.C.
- 1619 Jamestown farmers required to grow hemp
- 1850-1942 Cannabis listed in United States Pharmacopeia
- 1906-1937 Local, state, and federal regulation of cannabis enacted
- 1906-present Local, state, and federal efforts to end regulation initiated
- 1964 Δ<sup>9</sup>-Tetrahydrocannabinol (THC) identified
- 1970 classified as schedule I controlled substance in U.S.
- 1970s-present R&D of novel synthetic cannabinimetic agents
- 1985 FDA approves synthetic THC pharmaceutical agent dronabinol
- Late 1980s/Early 1990s endocannabinoid system defined



## Endocannabinoid System Basics

- **CB1 receptors**
  - Distributed throughout the brain
  - Activation affects the release of acetylcholine, L-glutamate, γ-aminobutyric acid, noradrenaline, dopamine and serotonin
  - Responsible for clinical effects on regulation of cognition, memory, motor activities, nociception, and nausea or vomiting
- **CB2 receptors**
  - Located peripherally in immune system tissues, B lymphocytes, peripheral nerve terminals, and the vas deferens.
  - Believed to participate in the regulation of immune responses and inflammatory reactions.



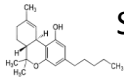
Goldfrank's Toxicologic Emergencies, 9<sup>th</sup> edition

## Proposed Therapeutic Uses for Cannabinoids

- |   |                              |
|---|------------------------------|
| Anxiety   | Migraine headaches           |
| Asthma  | Multiple sclerosis           |
| Depression  | Muscle spasticity and spasms |
| Epilepsy  | Neurological disorders       |
| Glaucoma  | Pain                         |
| Traumatic head injury   | Parkinson disease            |
| Insomnia  | Tourette syndrome            |
| Anorexia-cachexia syndrome secondary to AIDS *                      |                              |
| Resistant nausea and vomiting associated with cancer chemotherapy** |                              |

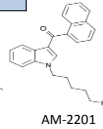
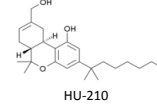
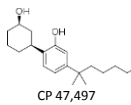
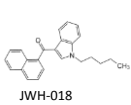
\*FDA approved indication for dronabinol

\*\*FDA approved indication for dronabinol & nabilone



## Synthetic Cannabinoids

THC	HU-210, HU-211	Raphael Mechoulam, Ph.D. Hebrew University
	JWH-018, JWH-073	John W. Huffman Ph.D. Clemson University
	CP 47,497	Charles Pfizer Pharmaceutical Company
	WIN 55,212-2	Sterling Winthrop Pharmaceuticals
	AM-2201	Alexandros Markiyannis Ph.D. Northeastern University



## Synthetic Cannabinoid Product Material



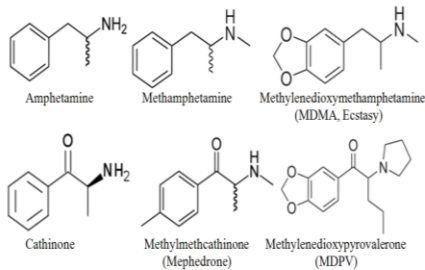
- 96 Hours of Fun Hell Anxiety and Insanity
- Stimulated, Alert, Socially Loose
- Most Devilish Powdered eVil
- I Went to Hell and I Saw the Abyss
- Vivid Hallucinations and Intense Paranoia
- Better than Meth
- Social Withdrawal, Stereotypy and Psychosis
- Seemingly Real Paranoid Hallucination Hell

## A Very Incomplete History of Cathinone

- Catha edulis (Khat, Qat) native to east Africa & Arabian Peninsula contains the phenethylamine alkaloid cathinone
- Centuries old history of use for its stimulant and mild euphoria effects
- Library of synthetic compounds derived from base structure, majority not fully investigated due to toxicities seen in early testing
- Mechanism of action postulated to involve varying degrees of release and blocked reuptake of dopamine, norepinephrine and serotonin



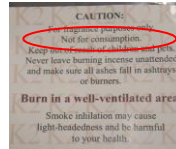
## Structural Similarity of Amphetamines and Cathinones





## Synthetic Cannabinoids

- 100s of different brand name products disguised as incense, potpourri, herbal smoke blends
- Commonly sold in sachets contain 3 grams of vegetable matter which are treated with one or more synthetic cannabinoids (but not always vegetable matter in appearance)
- Most commonly smoked, but reports of ingestion, insufflation, rectal and parenteral use.
- Cost of 3 grams is between \$20-50, utilized dose varies from user to user
- Original labeling listed multiple "herbal" compounds and always with some wording of "not for human consumption"



**"K2/Spice" = Synthetic Cannabinoids**

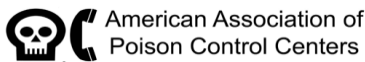
**"Bath Salts" = Synthetic Cathinones**

## Synthetic Cathinones

- 100s of different brand name products disguised as bath salts, plant food, or research chemicals
- Commonly sold in small jars or sachets containing 500 mg of white or brown powders.
- Most commonly insufflated or ingested, but reports of rectal and parenteral use.
- Cost of 500 mg is between \$20-50, utilized dose varies from user to user and from one specific agent to another
- Labeling typically with some wording of "not for human consumption"







## "Savvy Entrepreneurs"



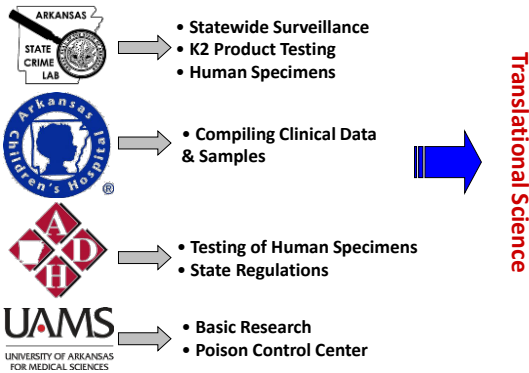
YEAR	Number of THC Homolog Calls
2010	2,905
2011	6,967
2012 As of August 31, 2012	4,221

YEAR	Number of Bath Salt Calls
2010	304
2011	6,133
2012 As of August 31, 2012	2,264

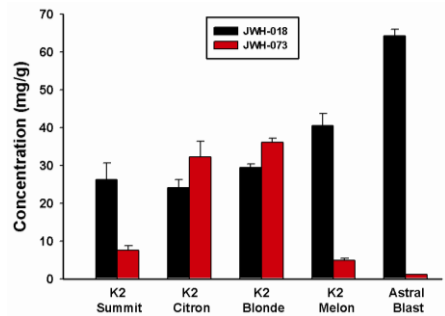
## Media Hysteria and Hype, or Cause for Concern?

- Fake Weed "K2" Can Cause Hallucinations Study Also Says Vomiting, Seizures Among Possible Reactions to Synthetic Drug 
- After Indianola teen's suicide, Iowa officials set sights on banning K2 
- Doctors concerned over possible link of K2, heart damage
- Killing "spice" before it kills again 
- Students Hospitalized After Smoking Synthetic Marijuana
- Synthetic drugs send thousands to ER 

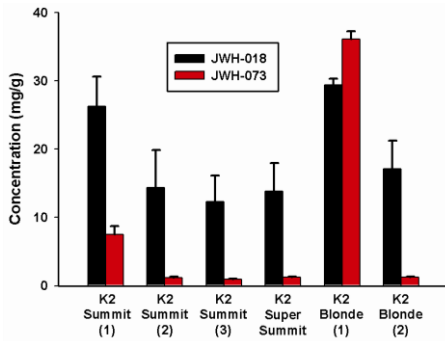
## Arkansas Designer Drug Workgroup



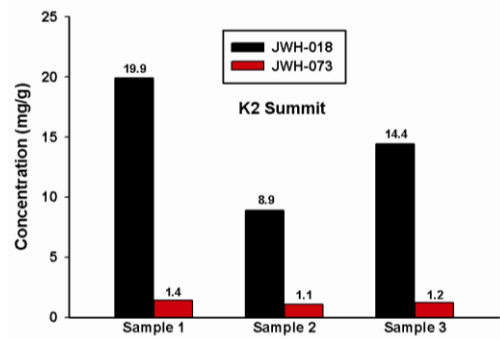
## Quantitative Study – Different Products



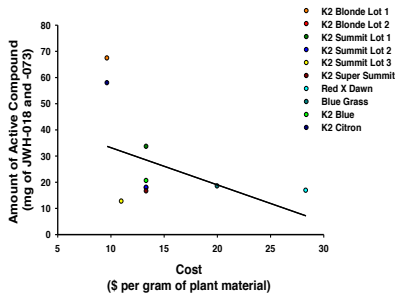
## Quantitative Study – Same Product, Different Lot



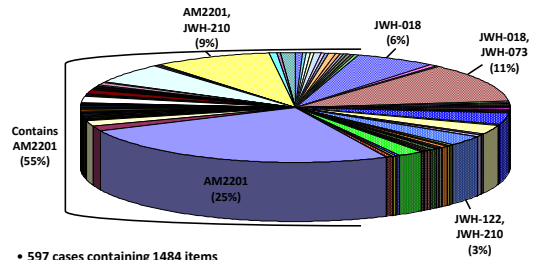
## Hot Spots



## Cost Correlation



## Composition of Synthetic Cannabinoid Products in Arkansas Forensic Samples

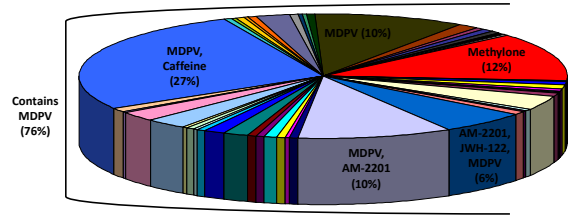


- 597 cases containing 1484 items
- 160 different combinations
- 14 synthetic cannabinoid compounds detected:  
JWH-018, JWH-019, JWH-073, JWH-081, JWH-122, JWH-203, JWH-210, JWH-250, AM694, AM2201, AM2233, RCS-4, RCS-4 C8 Analogue, RCS-8

## Designer Stimulant Products



## Composition of Designer Stimulant Compounds Products in Arkansas Forensic Samples



- 130 cases containing 254 items
- 12 stimulant compounds detected: 3,4-DMMC, 4-MEC, 4-MePPP, Butylone, BZP, FMC, MDPV, Mephedrone, Methylone, Pentecrone, PVP, TFMPP
- Other substances found in stimulant products: caffeine, synthetic cannabinoids, lidocaine, benzocaine, methamphetamine, levamisole

## Forensic Summary

- No Quality Assurance/Control:
  - Deceptive labeling
  - Compounds vary from product to product
  - Concentrations of the compounds vary within the package – “Hot Spots”
  - Concentrations of the compounds vary between different lots of the same products
  - Adulterants
  - New compounds ever emerging



## A Characterization of Synthetic Cannabinoid Exposures Reported to the National Poison Data System in 2010

(Hoyte CO, et al. Ann Emerg Med 2012 May 8. [Epub ahead of print])

Symptom	N=1,353 (%)
Tachycardia	541 (40)
Agitation/irritability	317 (23.4)
Vomiting	207 (15.3)
Drowsiness/lethargy	183 (13.5)
Confusion	164 (12)
Nausea	139 (10)
Hallucination/delusion	127 (9.4)
Hypertension	110 (8.1)
Dizziness/vertigo	99 (7.3)
Chest pain	64 (4.7)
Seizure	52 (3.8)

Treatment	N=1,353 (%)	Duration of clinical effects	N=907 (%)
IV fluid administration	343 (25.3)	Less than 8 hours	711 (78.4)
Benzodiazepines	217 (16)	Between 8 and 24 hours	151 (16.6)
Supplemental oxygen	79 (5.8)	More than 24 hours	44 (4.9)
Antiemetic	64 (4.7)		

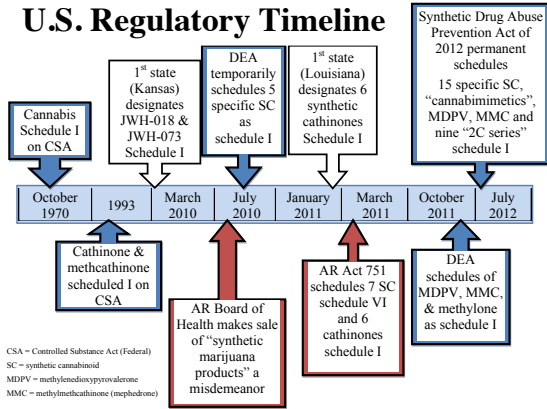
## Characterization of “Bath Salt” exposures reported to select U.S. Poison Centers

SYMPTOMS	Spiller HA, et al. (KY and LA) N=236	Murphy CM, et al. (NC) N=409	Forrester MB, et al. (TX) N=292
Agitation	194 (82.2%)	206 (50.4%)	57 (3.3%)
Tachycardia	132 (55.9%)	218 (53.3%)	45 (3.3%)
Hallucinations	94 (39.8%)	109 (26.7%)	17 (8.3%)
Confusion	83 (35.2%)		12 (3.3%)
Hypertension	41 (17.3%)	103 (25.2%)	19 (2.3%)
Chest pain	40 (16.9%)		7 (5.3%)
Mydriasis	31 (13.1%)		
CPK elevation	22 (9.3%)		
Vomiting			9 (4.4%)
TREATMENTS			
Benzodiazepine	125 (53%)	188 (46%)	38 (4.4%)
Sedation	antipsychotic = 47 (19.9%) propofol = 10 (4.2%)	55 (13.4%) haloperidol = 40 (9.8%)	6 (8.8%)
Alkalinization		16 (3.9%)	
Antihistamine		17 (4.2%)	
Intubation		15 (3.7%)	

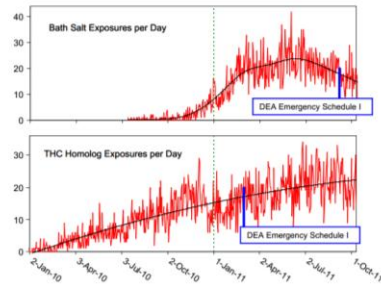
## Federal Analog Act of 1986



# U.S. Regulatory Timeline



# Daily U.S. Poison Center Call Volume



## Comparison of Acute Clinical Toxicity following "recreational dose"

### K2/Spice

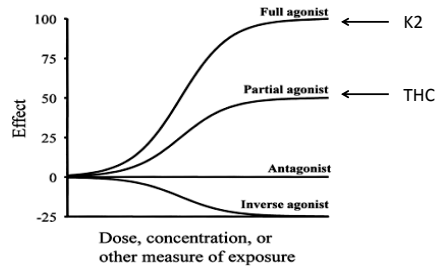
- Increased Heart Rate
- Altered mental status
- Anxiety
- Agitation
- Nausea/vomiting
- Tremor
- Pallor
- Hallucinations
- Seizures (infrequent)
- Dysrhythmia (infrequent)
- Renal failure (rare)
- Myocardial infarct (rare)

### Marijuana

- Increased Heart Rate
- Altered mental status
- Ataxia
- Decreased capacity to do complex tasks
- Injected conjunctiva

## "K2" vs. THC

Dose Response Relationships are not Equal



## Synthetic Cannabinoid Treatment Considerations

- ABCs
- Benzodiazepines
- Correct fluid/electrolytes
- Supportive care
- Contact regional poison center 1-800-222-1222

**Laboratory**

- CMP,
- CBC?
- EKG
- ABG?
- UA
- Standard urine tox screen?
- Specialized urine tox screen???

## Designer Simulant Clinical Concerns

- Tachycardia/Dysrhythmia
- Hypertension
- Mydriasis
- Fever
- Chest pain
- Agitation
- Hallucinations
- Fluid/Electrolyte balance
- Dystonia/Myoclonus/Catationia
- Seizures
- Extreme paranoia/delusions (may be prolonged >7 days)
- Rhabdomyolysis
- Sleep deprivation

## Designer Stimulant Treatment Considerations

- ABCs
- De-escalation techniques (if indicated)
- Benzodiazepines
- Benzodiazepines
- Benzodiazepines
- Benzodiazepines
- Antipsychotics ??
- Propofol ?
- Diphenhydramine (for clonus)
- External cooling
- Correct fluid/electrolytes
- Supportive care
- Contact regional poison center (1-800-222-1222)

Laboratory

- CMP, CBC
- CK, Troponins?
- EKG
- ABG?
- UA
- Standard urine tox screen?
- Specialized urine tox screen???

## Altered Mental Status Differential Diagnosis

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Poisoning/Drug</li> <li>• Withdrawal</li> <li>• Metabolic imbalance</li> <li>• Psychiatric</li> <li>• Trauma</li> </ul> | <ul style="list-style-type: none"> <li>• Cardiovascular</li> <li>• Seizure</li> <li>• Stroke</li> <li>• Infection</li> <li>• Tumor</li> </ul> |
|--|---|

## Pitfalls and Caveats

- First responder and Hospital management errors
- Variation in active agent
- Combination products
- Coingestants & adulterants
- Acute vs. Chronic vs. Acute-on-Chronic
- Product confusion

### Synthetic Cannabinoids

- |                                      |                         |
|--------------------------------------|-------------------------|
| Piperadines                          | Phenethylamines         |
| Phenazepam                           | Piperazines             |
| Methoxetamine                        | Krokodil (desomorphine) |
| Kratom ( <i>Mitragyna speciosa</i> ) | <i>Salvia divinorum</i> |

The paradigm of psychoactive substance use has radically changed and today if it walks, quacks, and looks like a duck it may not be a duck...  
Especially if someone is smoking its bill.



Questions?



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