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INNOVATION

**Involvement of Synthetic Cannabinoids
as Cause or Contributing Cause of Death**

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Chief Scientist, NMS Labs

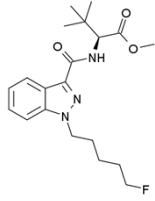
Disclosure

- Barry Logan is a salaried employee of NMS Labs, a commercial laboratory providing forensic testing services.

Synthetic Cannabinoids

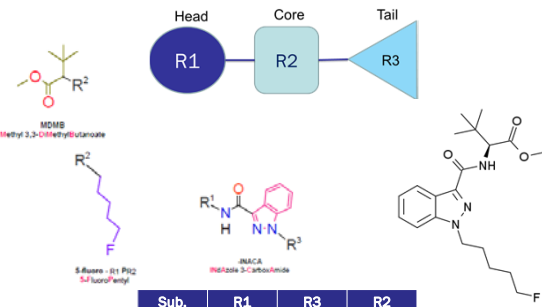
- 1982 – Chemists at Pfizer discovered cannabinoid activity of a new structural class.
- 1988 – Raphael Mechoulam at the Hebrew University synthesized benzopyran derivatives with cannabinoid activity.
- 1995 – John W Huffman synthesized a series of novel cannabinoid agonists at Clemson University.
- 2004 – These compounds began appearing in illicit drug products in Europe.
- 2009 – First SC seizure in the United States

What's in a Name?



methyl 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate

What's in Name?



Sub.	R1	R3	R2
5F-	MDMB	P	INACA

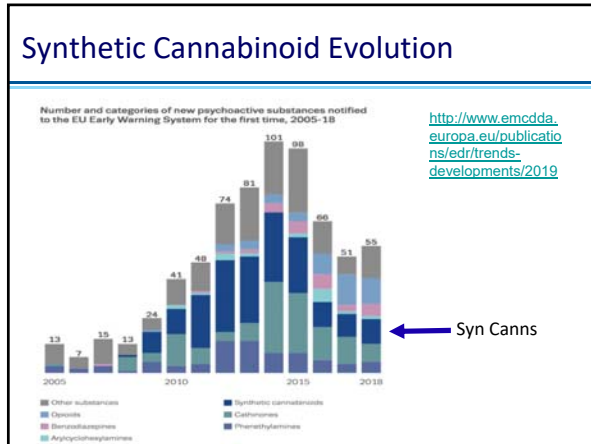
Naming the New Substances...

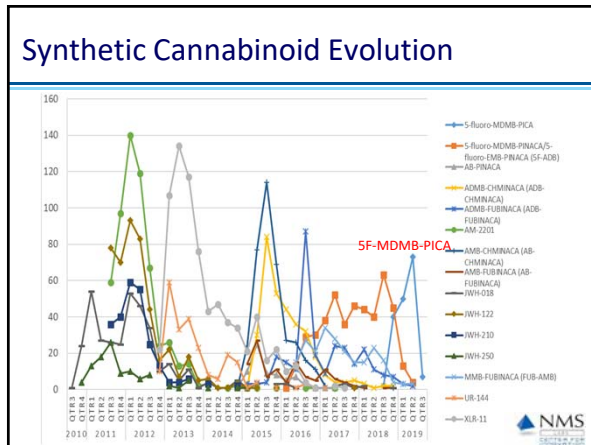
- o EMCDDA provides tool to visualize compounds

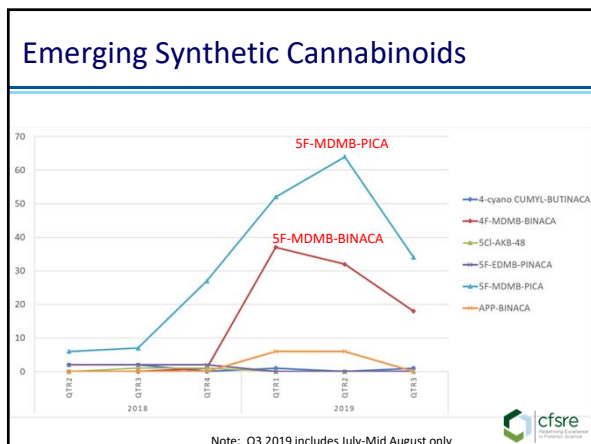


Over 620 new psychoactive substances are currently monitored by the EMCDDA through the EU Early Warning System, **169** of which are synthetic cannabinoid receptor agonists.

<http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids#panel2>






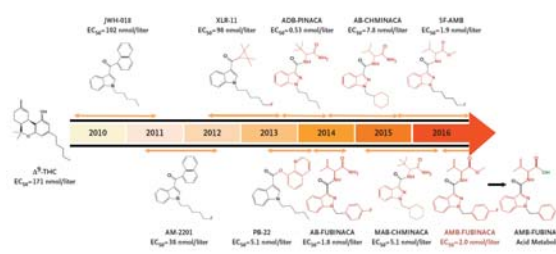


Synthetic Cannabinoid Evolution

Date Range	Major SC's
2010 - 2012	JWH-018, JWH-250, JWH-210, AM-2201
2013 - 2014	XLR-11, UR-144
2015 - 2016	AMB-CHMINACA, ADB-CHMINACA, ADB-FUBINACA
2017 - 2018	SF-ADB, FUB-AMB
2019	SF-MDMB-PICA, SF-MDMB-BINACA



Synthetic Cannabinoid Evolution



Adams AJ, Banister SD, Irizarry L, Trecki J, Schwartz M, Gerona R. "Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York. *N Engl J Med.* 2017 Jan 19;376(3):235-242

Synthetic Cannabinoid Toxicity

Organ system affected	Symptoms and signs
Central nervous system	Agitation, psychosis, irritability, seizures, sedation, coma, delirium, hallucinations, paranoia, anxiety, self-harm, psychomotor impairment
Cardiovascular	Tachycardia, hypertension, acute coronary syndrome, arrhythmia, chest pain, myocardial infarction
Pulmonary	Tachypnea, diffuse alveolar hemorrhages
Other	Nausea, vomiting, fevers, mydriasis, lack of convergence of gaze, acute kidney injury, hyperglycemia, hypokalemia, apoptotic cell death

Logan BK, Mohr ALA, Friscia M, Krotulski AJ, Papsun DM, Kacinko SL, Roper-Miller JD, Huestis MA. Reports of Adverse Events Associated with Use of Novel Psychoactive Substances, 2013-2016: A Review. *J Anal Toxicol.* 2017 Sep 1;41(7):573-610.

Cognitive Impairment

Blood Synthetic Cannabinoid Concentrations in Cases of Suspected Impaired Driving.
Yeakel JK, Logan BK. J Anal Toxicol. 2013 Oct;37(8):547-51.

- 12 cases of Suspected impaired driving involving synthetic cannabinoids.
- Attitude of the drivers was cooperative and relaxed, speech was slow and slurred, coordination was poor.
- Pulse and blood pressure were generally elevated.
- The most consistent sign noted was a marked lack of convergence in all cases where it was assessed.
- JWH-018 (n=4), 0.1-1.1ng/mL; JWH-081 (n=2) qualitative only; JWH-122 (n=3) 2.5ng/mL; JWH-210 (n=4) 0.1ng/mL; JWH-250 (n=1) 0.38ng/mL; AM-2201 (n=6) 0.43 – 4.0ng/mL.

Cognitive Impairment

Differential physiological and behavioral cues observed in individuals smoking botanical marijuana versus synthetic cannabinoid drugs.
Chase PB, Hawkins J, Mosier J, Jimenez E, Boesen K, Logan BK, Walter FG.

- 16 synthetic cannabinoid and 25 marijuana cases.
- AM-2201, JWH-022, JWH-122, JWH-018 detected.
- Drivers under the influence of synthetic cannabinoids were more frequently impaired with confusion, disorientation, and incoherent, slurred speech than drivers under the influence of marijuana in this population evaluated by DREs.

Cognitive Impairment

Select Other SC Driving Impairment Case Series:

- Kraemer M, Fels H, Dame T, Musshoff F, Halter S, Mogler L, Hess C, Madea B, Maas A. Mono-/polyintoxication with 5F-ADB: A case series. *Forensic Sci Int.* 2019 Aug;301:e29-e37.
- McCain KR, Jones JO, Chilbert KT, Patton AL, James LP, Moran JH. Impaired Driving Associated with the Synthetic Cannabinoid 5F-ADB. *J Forensic Sci Criminol.* 2018 Aug;6(1).
- Kaneko S. Motor vehicle collisions caused by the 'super-strength' synthetic cannabinoids, MAM-2201, 5F-PB-22, 5F-AB-PINACA, 5F-AMB and 5F-ADB in Japan experienced from 2012 to 2014. *Forensic Toxicol.* 2017;35(2):244-251.
- Peterson BL, Couper FJ. Concentrations of AB-CHMINACA and AB-PINACA and Driving Behavior in Suspected Impaired Driving Cases. *J Anal Toxicol.* 2015 Oct;39(8):642-7.
- Louis A, Peterson BL, Couper FJ. XLR-11 and UR-144 in Washington state and state of Alaska driving cases. *J Anal Toxicol.* 2014 Oct;38(8):563-8.

Synthetic Cannabinoid Toxicity

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Syn Cann Deaths

Synthetic Cannabinoid-Related Illnesses and Deaths.

Trecki J, Gerona RR, Schwartz MD. N Engl J Med. 2015 Jul 9;373(2):103-7.

- Use of synthetic cannabinoids particularly by younger and inexperienced users, has led to multiple clusters of cases of adverse health effects and deaths.
- Effects include excited delirium, acute kidney injury, seizures, psychosis, hallucinations, cardiotoxic effects, coma, and death — with some users dying before they could reach an emergency department.
- ADB-FUBINACA, AB-CHMINACA, AB-PINACA, 5F-PB-22
- 18 Deaths, and >600 cases of hospitalization.

Syn Cann Deaths

Synthetic cannabinoid drug use as a cause or contributory cause of death.

Labay LM, Caruso JL, Gilson TP, Phipps RJ, Knight LD, Lemos NP, McIntyre IM, Stoppacher R, Tormos LM, Wiens AL, Williams E, Logan BK. Forensic Sci Int. 2016 Mar;260:31-39.

- Deaths are being attributed to synthetic cannabinoids, with the highest risk areas being behavioral toxicity resulting in excited delirium, trauma or accidents and as contributing factors in subjects with pre-existing cardiopulmonary disease.
- Insufficient information exists to correlate blood synthetic cannabinoid concentrations to effect.
- In the absence of other reasonable causes, the drugs should be considered as a cause or contributory cause of death based on history and circumstances with supporting toxicological data.

Syn Cann Deaths

Characteristics and circumstances of synthetic cannabinoid-related death.

Darke S, Dufloy J, Farrell M, Peacock A, Lappin J. Clin Toxicol (Phila). 2019 Aug 7:1-7. [E-Pub ahead of print].

- Retrospective study of cases in Australia in which synthetic cannabinoid use was a mechanism contributory to death (n = 55)
- Information was collected on cause of death, demographics, drug history, circumstances of death, toxicology and organ pathology.
- The most frequent synthetic cannabinoids were the indazolecarboxamides (61.8%), especially AB-CHMINACA (38.2%).
- While acute toxicity was the most common cause of death, cardiovascular disease was prominent.

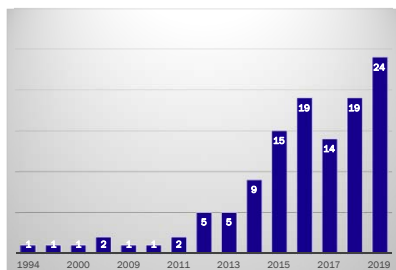
Syn Cann Deaths

Select Other SC Related Death Case Series:

- Adams AJ, Banister SD, Irizarry L, Trecki J, Schwartz M, Gerona R. "Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York. N Engl J Med. 2017 Jan 19;376(3):235-242.
- Al-Matrouk A, Alqallaf M, AlShemmeri A, BoJbarah H. Identification of synthetic cannabinoids that were seized, consumed, or associated with deaths in Kuwait in 2018 using GC-MS and LC-MS-MS analysis. Forensic Sci Int. 2019 Sep 13;303:109960.
- Chan S, Wu J, Lee B. Fatalities related to new psychoactive substances in Singapore-A case series. Forensic Sci Int. 2019 Jul 26:109892.
- Boland DM, Reidy LJ, Seither JM, Radtke JM, Lew EO. Forty-Three Fatalities Involving the Synthetic Cannabinoid, 5-Fluoro-ADB: Forensic Pathology and Toxicology Implications. J Forensic Sci. 2019 Jun 18 [Epub ahead of print].
- Kraemer M, Fels H, Dame T, Musshoff F, Halter S, Mogler L, Hess C, Madea B, Maas A. Mono-/polyintoxication with 5F-ADB: A case series. Forensic Sci Int. 2019 Aug;301:e29-e37.

Syn Cann Deaths

Publications in PubMed by year:
"Synthetic cannabinoids" and "Death"



Conclusions

- Synthetic cannabinoids continue to be popular.
- Novel, high potency compounds still appearing.
- Additional resources for testing available.
- Mounting evidence of synthetic cannabinoid involvement in deaths.
- Behavioral toxicity contributes to traumatic and traffic deaths.
- Cardiac compromise is a frequent contributing cause in these cases.