

Recreational Synthetic Cannabinoids: History and Deleterious Neuropsychiatric Effects

December 6, 2020

Outline

- Introduction
- Chemistry
- Background and origins of use
- The regulation conundrum
 - Efforts to elude
- Scope of the problem
- Appearance
- Desired use effects
- Health effects



Image of *K2* from the DEA

Introduction

- Group of recreational illicit substances
- Collectively known as “synthetic cannabinoids”
- Represent a recent, and worsening public health concern



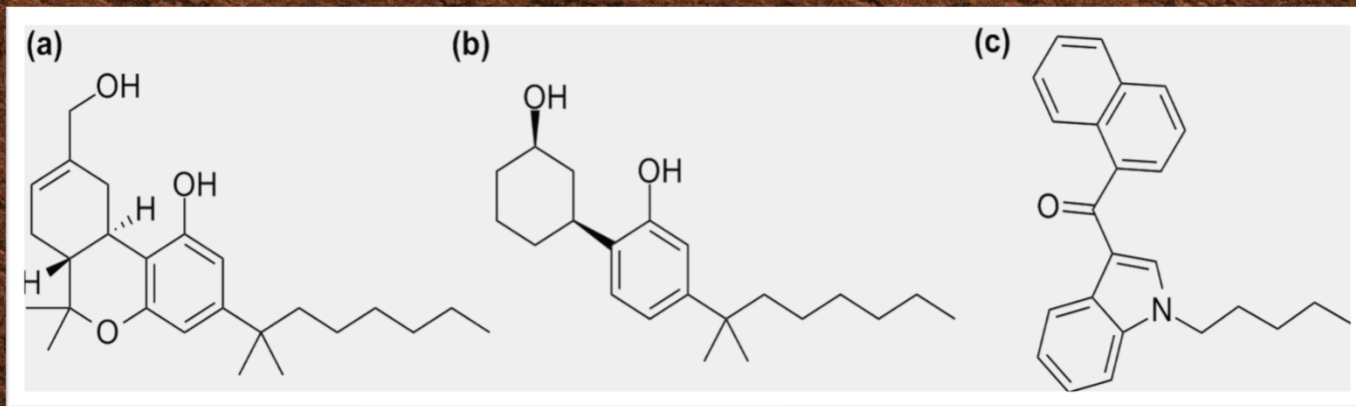
Introduction continued

- This is *not* dronabinol/Marinol
- Difficult to categorize
- Physically, neurologically, psychiatrically dangerous
- Socially dangerous
- Common



Chemistry

- One early compound was HU-210, synthesized in Israel in 1988
- Different citations indicate it is at least 100x more potent than Δ^9 -tetrahydrocannabinol (THC)



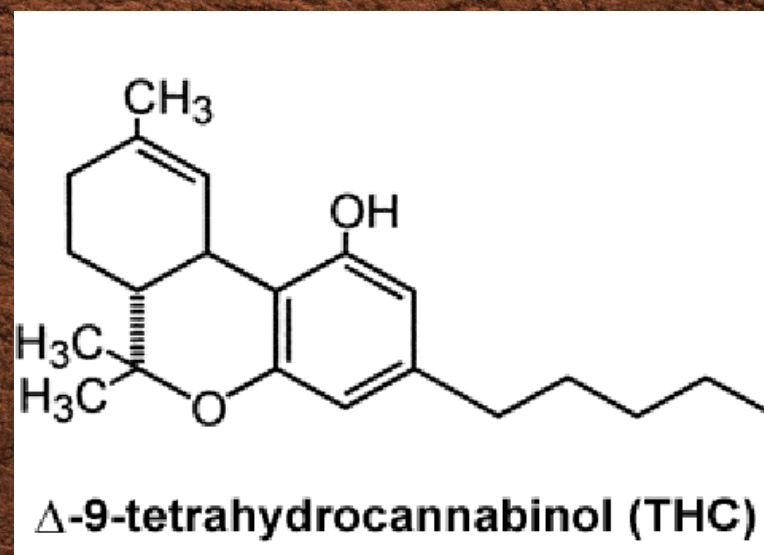
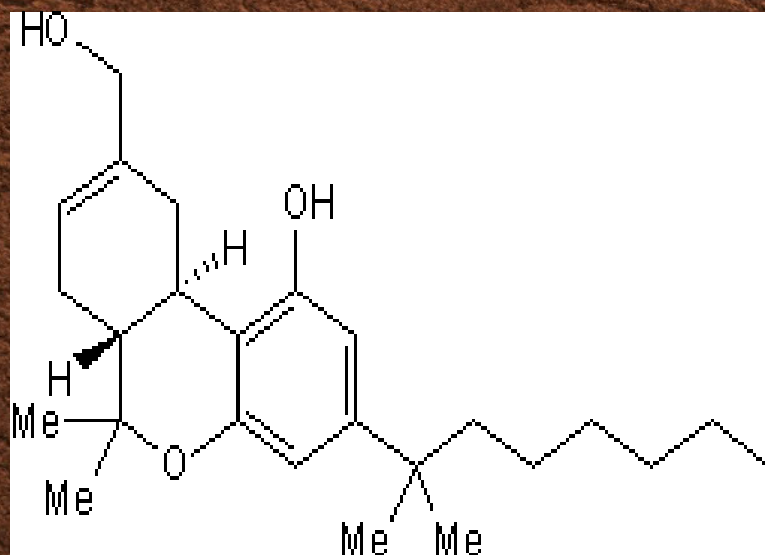
HU-210

CP-47,497

JWH-018

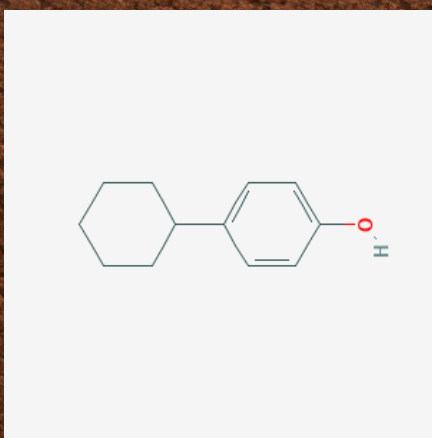
Chemistry, continued

-HU-210 is a classical cannabinoid, or structural analogue of THC

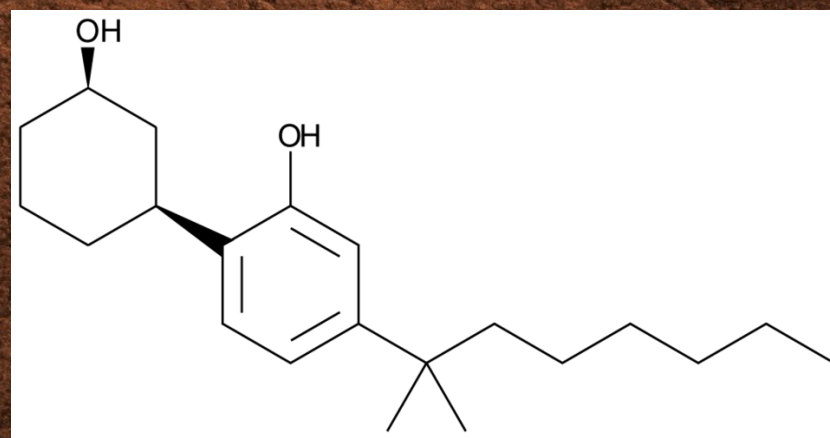


Chemistry, continued

- Pfizer also synthesized a group of “non-classical” cannabinoids, called cyclohexoxyphenols
- The “CP compounds”
- These were developed as potential analgesics, in the 1980s



A CP generally



CP 47,497 (from a supplier website)

Background and origins of use

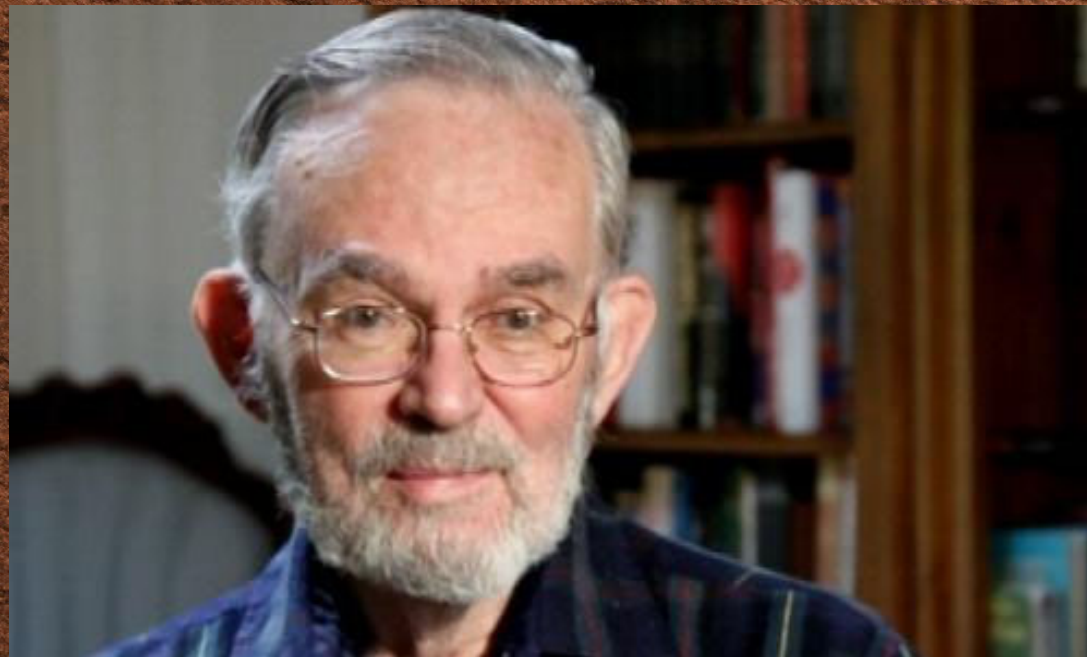
- Early to mid-1990s, researcher John W. Huffman spearheaded the design and synthesis of 300+ synthetic cannabinoid and “cannabimimetic” compounds
- Published his work

Huffman, John W et al. “Synthesis and pharmacology of 1-methoxy analogs of CP-47,497.” *Bioorganic & medicinal chemistry* vol. 18,15 (2010): 5475-82.
doi:10.1016/j.bmc.2010.06.054

Background and origins of use, continued

The modern era of the study of cannabinoids began with the elucidation of the structure of the principal psychoactive ingredient in marijuana, Δ^9 -tetrahydrocannabinol (Δ^9 -THC, **1**), by Gaoni and Mechoulam.¹ Subsequently, a number of analogs of **1** were synthesized and comprehensive structure-activity relationships (SAR) were developed based upon the Δ^9 -THC template.²⁻⁴ In the course of the development of analgesics derived from the potent synthetic cannabinoid, (-)-9-nor-9 β -hydroxyhexahydrocannabinol (HHC, **2**), a series of structurally modified analogs of **2** were prepared.⁵⁻⁷ Although useful analgesics were not developed, a series of non-traditional cannabinoids was developed in which the oxygen containing pyran ring of THC was removed to provide a bicyclic system that retained the phenolic hydroxyl group of THC and the 9-hydroxyl of HHC.⁸ The SAR for traditional cannabinoids specifies maximum potency with a 1,1-dimethylheptyl substituent at the 3-position of the aromatic ring and an equatorial β -orientation of the 9-hydroxyl group.⁸ These SAR are also valid for these bicyclic non-traditional cannabinoids and the least complex molecule that fulfilled these requirements was CP-47,497 (**3**, DMH = 1,1-dimethylheptyl), which was found to be more potent than THC *in vivo*. A hydroxypropyl group at C-4 of the cyclohexanol ring, as in CP-55,940 (**4**), led to enhanced potency and in 1988 [³H]-CP-55,940 was employed by Howlett's group to identify a cannabinoid receptor in rat brain.⁹ This G-protein-coupled, transmembrane receptor is now designated as the CB₁ receptor and is expressed primarily in the central nervous system.¹⁰⁻¹²

Background and origins of use, continued



John W. Huffman

Background and origins of use, continued

- Appears to have been duplicated by a chemist in China
- Then first reported in illicit “herbal high” products in early 2000s in Europe
- Also NPS in India, Poland, and the Netherlands



Background and origins of use, continued

- People are going to find ways to use cannabis, even if it is illegal



Former governor of California

The regulation conundrum

- As humans, we understand the spirit of:

 - “Herbal high”

 - “Synthetic cannabinoid”

- Plant-based taxonomies fail

- Chemistry-based taxonomies fall short

The regulation conundrum, continued

-From an LDH press release

“Gov. Jindal and State Officials Ban New Synthetic Marijuana Compound

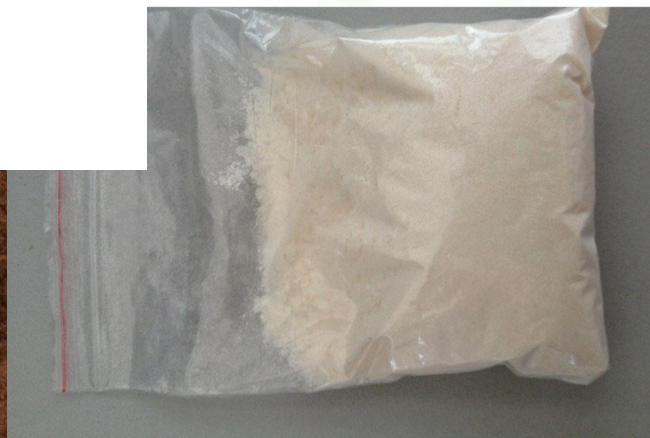
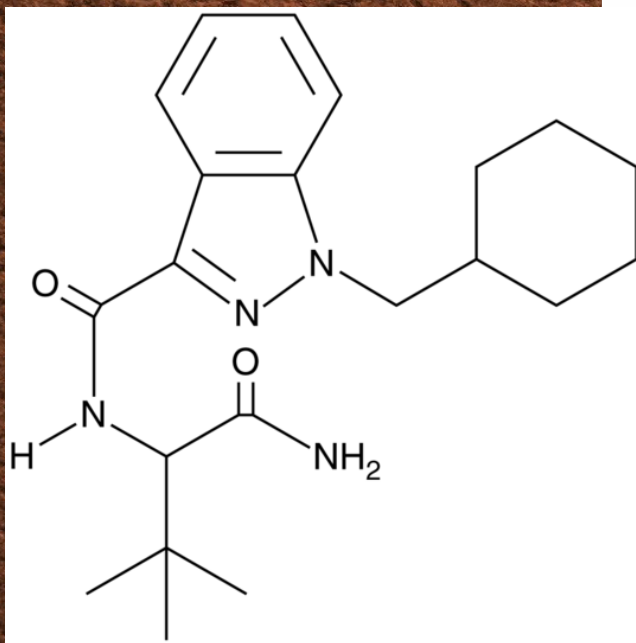
More than 125 Baton Rouge residents treated for issues caused by dangerous designer drugs

October 29, 2014

Gov. Bobby Jindal and officials with the Louisiana Department of Health and Hospitals (DHH), and Louisiana State Police (LSP) announced the ban of a new synthetic marijuana compound called "MAB-CHMINACA" today...”

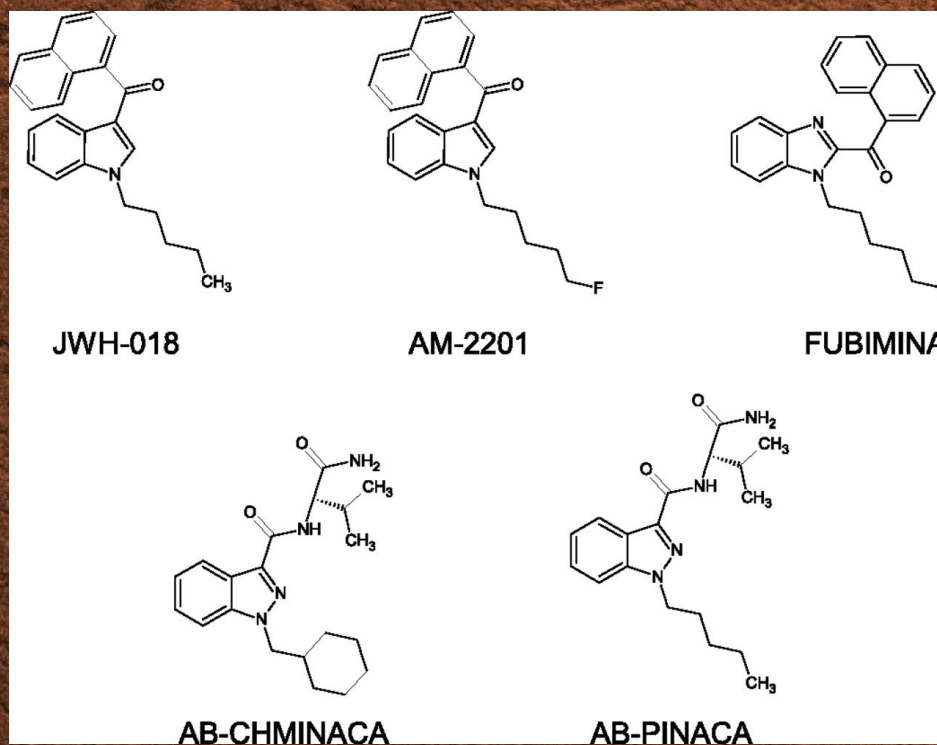
The regulation conundrum, continued

-But that's just MAB-CHMINACA



The regulation conundrum, continued

-Small chemical manipulations



The regulation conundrum, continued

-112th Congress and President Obama signed sTHC regulation into law in 2012

SEC. 1152. ADDITION OF SYNTHETIC DRUGS TO SCHEDULE I OF THE CONTROLLED SUBSTANCES ACT. (a) CANNABIMIMETIC AGENTS.—Schedule I, as set forth in section 202(c) of the Controlled Substances Act (21 U.S.C. 812(c)) is amended by adding at the end the following:

“(d)(1) Unless specifically exempted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of cannabimimetic agents, or which contains their salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation.

“(2) In paragraph (1): “(A) The term ‘cannabimimetic agents’ means any substance that is a cannabinoid receptor type 1 (CB1 receptor) agonist as demonstrated by binding studies and functional assays within any of the following structural classes:

The regulation conundrum, continued

“(i) 2-(3-hydroxycyclohexyl)phenol with substitution at the 5-position of the phenolic ring by alkyl or alkenyl, whether or not substituted on the cyclohexyl ring to any extent. S. 3187—139

“(ii) 3-(1-naphthoyl)indole or 3-(1-naphthylmethane)indole by substitution at the nitrogen atom of the indole ring, whether or not further substituted on the indole ring to any extent, whether or not substituted on the naphthoyl or naphthyl ring to any extent.

“(iii) 3-(1-naphthoyl)pyrrole by substitution at the nitrogen atom of the pyrrole ring, whether or not further substituted in the pyrrole ring to any extent, whether or not substituted on the naphthoyl ring to any extent.

“(iv) 1-(1-naphthylmethylene)indene by substitution of the 3-position of the indene ring, whether or not further substituted in the indene ring to any extent, whether or not substituted on the naphthyl ring to any extent.

“(v) 3-phenylacetylindole or 3-benzoylindole by substitution at the nitrogen atom of the indole ring, whether or not further substituted in the indole ring to any extent, whether or not substituted on the phenyl ring to any extent.

The regulation conundrum, continued

“(B) Such term includes—

“(i) 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3- hydroxycyclohexyl]-phenol (CP-47,497);

“(ii) 5-(1,1-dimethyloctyl)-2-[(1R,3S)-3- hydroxycyclohexyl]-phenol (cannabicyclohexanol or CP- 47,497 C8-homolog);

“(iii) 1-pentyl-3-(1-naphthoyl)indole (JWH-018 and AM678);

“(iv) 1-butyl-3-(1-naphthoyl)indole (JWH-073);

“(v) 1-hexyl-3-(1-naphthoyl)indole (JWH-019);

“(vi) 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200);

“(vii) 1-pentyl-3-(2-methoxyphenylacetyl)indole (JWH- 250);

“(viii) 1-pentyl-3-[1-(4-methoxynaphthoyl)]indole (JWH-081);

“(ix) 1-pentyl-3-(4-methyl-1-naphthoyl)indole (JWH- 122);

“(x) 1-pentyl-3-(4-chloro-1-naphthoyl)indole (JWH- 398);

The regulation conundrum, continued

“(xi) 1-(5-fluoropentyl)-3-(1-naphthoyl)indole (AM2201);

“(xii) 1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole (AM694);

“(xiii) 1-pentyl-3-[(4-methoxy)-benzoyl]indole (SR-19 and RCS-4);

“(xiv) 1-cyclohexylethyl-3-(2-methoxyphenylacetyl)indole (SR-18 and RCS-8); and

“(xv) 1-pentyl-3-(2-chlorophenylacetyl)indole (JWH-203).”.

The regulation conundrum, continued

-The DEA has 43 sTHCs listed on Schedule I

In addition there are many other synthetic cannabinoids that meet the definition for "cannabimimetic agent" under the Controlled Substances Act and thus are Schedule I substances.

There are many synthetic cannabinoid substances that are being sold as "incense," "potpourri," and other products that are not controlled substances. However, synthetic cannabinoids may be subject to prosecution under the Controlled Substance Analogue Enforcement Act which allows noncontrolled drugs to be treated as Schedule I controlled substances if certain criteria can be met. The DEA has successfully investigated and prosecuted individuals trafficking and selling these dangerous substances using the Controlled Substance Analogue Enforcement Act.

Scope of the matter

- In 2009, only two types of recreational synthetic cannabinoids were reported to the DEAs National Forensic Laboratory Information System (NFLIS)
- Has expanded to 84 reported to NFLIS by 2015
- One source claims there are now over 500 novel psychoactive sTHC variants

Scope of the matter, continued

-As of February 1, 2020, NIH estimate of synthetic cannabis use patterns in secondary school students (past year use):

- 2.70% of eighth graders
- 2.60% of tenth graders
- 3.30% of twelfth graders

Scope of the matter, continued

- 2017 NIH report showed 0.5% of American college students, and 2.4% of American non-college young adults used sTHC in past year

Scope of the matter, continued

- 2020 DEA report showed most NFLIS reports for Louisiana involved sTHC or synthetic cathinones

The findings revealed that Louisiana submitted the majority of reports for synthetic cannabinoid substance and synthetic cathinones substance for 2013 to 2017.

Appearance

- Typically a liquid, or a crystalline powder
- Commonly sprayed onto dried plant material for smoking



Appearance, continued



From an Indonesian raid in 2020

Appearance, continued



A small lab raided in Sunset Louisiana, in 2014
Six pounds of sTHC, worth about \$27,000.00

Appearance, continued



Larger lab raided in Houston, in 2013

"100% Buzz"

"Kush,"

"Klimax"

"Serenity Now"



Appearance, continued

- With the contemporary advent of e-Cigs and vaping, it can also be inhaled as a vaporized liquid



Ostensibly these are four “CBD” vapes

Appearance, continued

- 2019 Associated Press study of 30 such products
- 10 contained a synthetic cannabinoid
- 22 contained little to no actual CBD



Appearance, continued



Natural cannabis vapes

-Recall, if it can be smoked or vaped...

Desired effects

- "The high is better" (than natural marijuana)
- "It's stronger" (than natural marijuana)
- "I could pass my tests" (UDS)
- "The Army didn't test for it"
- "Makes me forget"
- "I like it"

Desired effects, continued

- Physiological effects not definitively settled
- Appears that Δ^9 -THC functions as a partial agonist in the endocannabinoid receptor system, with effects at both type 1 and type 2 (CB1R, CB2R) receptors
- Net acute effect includes increased dopaminergic activity in seemingly in the prefrontal cortex, striatum, and nucleus accumbens

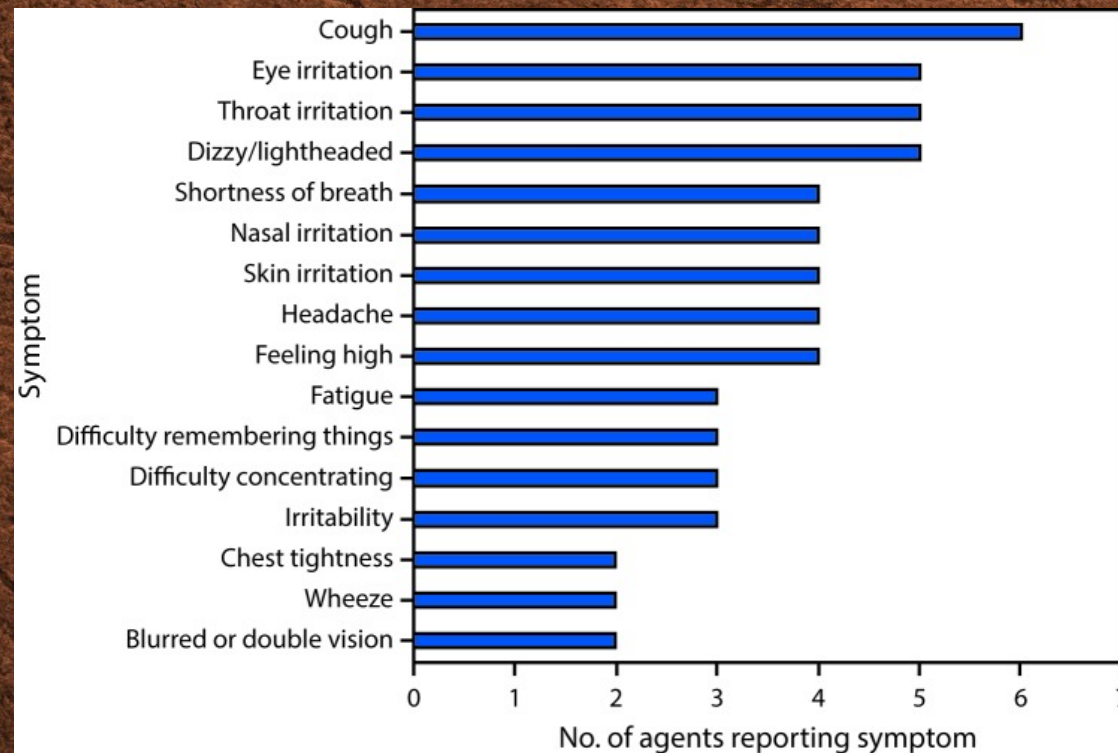
Risks generally

- Production issues
- Consistency
- Purity
- Potency
- Strength
- Inadvertent adulterants
- Intentional adulterants



Risks, generally, continued

- In one small cohort of law enforcement officers in a raid, numerous ill effects were reported



Nevada, 2014

Risks to the user

- Delirium

- Alteration of consciousness

- Agitation

- Confusion

- Aggression

- Reactive violence

- Unprovoked violence

- Instrumental violence

- Irrational behavior

Risks to the user, continued

- Amnestic symptoms
 - Acute cognitive impairment
 - Marked inattention
 - Marked concentration impairment



Groton, Connecticut

Risks to the user, continued

- Psychotic symptoms
 - Delusions
 - Disorganization
- Perceptual disturbances:
 - Alteration of time
 - Hyperesthesia
 - Tactile hallucinations
 - Visual hallucinations

Risks to the user, continued

- Mood and anxiety symptoms
 - Sedation
 - Insomnia
 - Depression
 - Anger
 - Irritability
 - Panic



Lake Charles 2018

Risks to the user, continued

- Behavioral constellations:
 - Suicidality
 - Homicidality
 - Compulsive nudity
 - Scatolia/coprophilia



Risks to the user, continued

- Neurological:
 - Dizziness
 - Dyscoordination
 - Ataxia
 - Seizure
 - CVA



17-year-old in Cypress, TX

Risks to the user, continued

-General:

- Nausea
- Vomiting
- Aspiration
- Respiratory distress
- Tachypnea
- Tachycardia
- Hypertension
- Myocardial infarction

Risks to the user, continued

-General:

- Hypokalemia (from emesis)
- Rhabdomyolysis
- Hyperkalemia (from rhabdomyolysis)
- Renal damage
- Bleeding
- Stress to endometrial stromal cells
without effect on apoptosis

Risks to the user, continued

- General:
- Death



In conclusion

- Relatively Recent
- Benign origins
- Rapidly maturing designer drug space
 - Continues to be motivation to use, and to produce/sell
- sTHC is here in LA
- sTHC is very risky to the brain, and to the user generally

Questions?



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Industry affiliations:

Eisai	Dayvigo Speaker Bureau	2020-present
Intra-Cellular Therapies	Caplyta Mindset Speaker Bureau	2020-present
Neurocrine Pharmaceuticals	Ingrezza Peer to Peer Speaker Bureau	2020-present
Alkermes	Expert Speaker	2016-present

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