STATEMENT OF

JORDAN TRECKI, PH.D.
PHARMACOLOGIST
DRUG AND CHEMICAL EVALUATION SECTION
DIVERSION CONTROL DIVISION
DRUG ENFORCEMENT ADMINISTRATION

BEFORE THE

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PRESENTED

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Introduction

Synthetic cannabinoids represent a sub-class of drugs commonly referred to as New Psychoactive Substances (NPS). Along with cathinones (also referred to as 'bath salts') and fentanyl-related substances, abuse of synthetic cannabinoids causes serious adverse effects including excited delirium, agitation, seizures, cardiac arrest, multi-organ failure and death amongst many others[1,2,3,4]. These drugs are trafficked to youth, those in drug rehab facilities[5], the homeless, users attempting to evade a positive drug screen and many other demographics and age groups. Illicit manufacturers of synthetic cannabinoids continue to make small chemical modifications while retaining the pharmacological effects users seek in an attempt to avoid law enforcement detection. Data from the patent and scientific literature for structures with psychoactive effects have given clandestine laboratories the blueprints to produce hundreds of synthetic cannabinoids for supplying the illicit market. Thousands of new compounds are likely to be produced and subsequently introduced to unsuspecting users. Legitimate pharmaceutical research, with the positive goal of finding new therapeutic drugs and targets to alleviate disease symptoms[6], has been exploited thereby resulting in widespread overdose clusters and individual deaths across the country that has only grown in number and severity since the first United States reports in 2010 and 2011. Marketed with street names including "synthetic marijuana," "Spice," "K2" and "Mojo," manufacturers lace an inert plant material with a synthetic cannabinoid, and dealers assure users that the effects are similar to marijuana. The consequences of ingesting these chemicals is a pathway to addiction with debilitating and often long lasting side effects, as well as the possibility of death.

Novel synthetic cannabinoids continue to be introduced into the illicit drug market in an attempt to circumvent current drug controls within the United States. These substances continue to pose a challenge for law enforcement, hospital staff and forensic and toxicological laboratories. Synthetic cannabinoids encountered on the illicit market produce a pharmacological effect similar to delta-9-tetrahydrocannabinol (THC) as demonstrated by basic research, along with many more serious adverse effects as described in case reports following their abuse. Traffickers of synthetic cannabinoids are typically prosecuted for violating the Controlled Substances Act and Controlled Substances Analogue Enforcement Act. Prosecution of

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[1] M.D. Schwartz, J. Trecki, L.A. Edison, A.R. Steck, J.K. Arnold & R.R. Gerona, *A Common Source Outbreak of Severe Delirium Associated with Exposure to the Novel Synthetic Cannabinoid ADB-PINACA*, 48 Journal of Emergency Medicine,573-80 (2015).

[2] J. Trecki, R.R. Gerona & M.D. Schwartz, *Synthetic cannabinoid-related illnesses and deaths*, 373 New England Journal of Medicine, 103-107 (2015).

[3] J.A. Tyndall, R. Gerona, G. De Portu, J. Trecki, J. Lucas, J. Slish, K. Rand, L. Bazydlo, M. Holder, M.F. Ryan, P. Myers, N. Iovine, M. Plourde, E. Weeks, J.R. Hanley, G. Endres, D. St Germaine, P.J. Dobrowolski & M. Schwartz, *An Outbreak of Acute Delirium from Exposure to the Synthetic Cannabinoid AB-CHMINACA*, 53 Clin Toxicol (Phila), 950-6, (2015).

[4] A.J. Adams, S.D. Banister, L. Irizarry, J. Trecki, M. Schwartz & R. Gerona, *"Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York*, 376 New England Journal of Medicine, 235-242 (2017).

[5] E.E. Bonar, L. Ashrafioun & M.A. Ilgen, *Synthetic Cannabinoid Use Among Patients in Residential Substance Use Disorder Treatment: Prevalence, Motives, and Correlates*, 143 Drug and Alcohol Dependence, 268-71 (2014).

[6] J.M. Frost, M.J. Dart, T.R. Tietje, T.R. Garrison, G.K. Grayson, A.V. Daza, O.F. El-Kouhen, B.B. Yao, G.C. Hsieh, M. Pai, C.Z. Zhu, P. Chandran, & M.D. Meyer, *Indol-3-ylcycloalkyl ketones: effects of N1 substituted indole side chain variations on CB2 cannabinoid receptor activity*, 53 Journal of Medicinal Chemistry, 295-315.

individuals involved in violations the Analogue Enforcement Act often requires expert testimony in the court by chemists and pharmacologists at both trial and sentencing.

Background

Synthetic cannabinoids are substances synthesized in laboratories and designed to mimic the biological effects of THC, the main psychoactive ingredient in marijuana. It is believed synthetic cannabinoids were first introduced on the designer drug market in several European countries as "herbal incense" before the initial encounter in the United States by U.S. Customs and Border Protection (CBP) in November 2008. From 2009 to the present, the law enforcement encounters and abuse of synthetic cannabinoids has increased in the United States. Law enforcement evidence indicates that synthetic cannabinoids are applied onto plant material and in other designer drug products intended for human consumption.

Based on law enforcement seizures, case reports, hospital admissions and medical examiner data, the use of synthetic cannabinoids has led to addiction and irrefutable harm to the users, their families and the communities surrounding them. The DEA has temporarily scheduled 23 synthetic cannabinoids to date to avoid imminent hazard to the public safety. Congress passed legislation in 2012 controlling 15 additional synthetic cannabinoids.[7] The American Association of Poison Control Centers continues to publish data from thousands of calls each year regarding adverse effects experienced following the abuse of synthetic cannabinoids containing products.[8]

As observed by the DEA and CBP, synthetic cannabinoids originate from foreign sources, such as China. Bulk powder substances are smuggled via common carrier into the United States and find their way to clandestine designer drug product manufacturing operations located in residential neighborhoods, garages, warehouses, and other similar destinations throughout the country. Based on law enforcement encounters, spraying or mixing the synthetic cannabinoids with plant material provides a vehicle for the most common route of administration—smoking (using a pipe, a water pipe, or rolling the drug-laced plant material in cigarette papers). However, with the large number of synthetic cannabinoids on the illicit market, it is difficult for an end user to accurately know which substance is applied to the product they obtained, as manufacturers attempt to evade law enforcement by changing to a new chemical with similar pharmacological properties.

Pharmacological Effects

THC is the primary psychoactive component of marijuana. Pharmacological effects of THC are thought to be mediated through at least two distinct receptors designated as CB1 and CB2. THC has been shown to have a similar binding affinity for both cannabinoid receptors, while acting as a partial agonist at these receptors. Research has shown that CB1 receptors are

[7] Section 1152 of Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112-144, July 9, 2012.

[8] American Association of Poison Control Centers, "Synthetic Cannabinoids," http://www.aapcc.org/alerts/synthetic-cannabinoids/ (reporting 1,497 exposures from January 1, 2017 to September 2017, and reporting that in 2015 there were 7,794 reported exposures).

found predominantly in the brain and the binding of a substance, like THC, to the CB1 receptor and subsequent activation of the CB1 receptor, lead to the psychoactive effects commonly observed following the ingestion of marijuana.

Both preclinical and clinical studies have demonstrated that THC possesses the attributes associated with drugs of abuse. THC is an effective reinforcer in laboratory animals, including primates and rodents. These animal studies predict and support the observations that THC, whether smoked as marijuana or administered by other routes, produces reinforcing effects in humans. Such reinforcing effects can account for repeated use and ultimately abuse.

THC can be obtained from two different sources: as a substance produced within the marijuana plant (organic) or produced synthetically, such as in a laboratory or pharmaceutical company. Regardless of the source, organic and synthetic THC have the same chemical structure and pharmacological effects.

In terms of pharmacological effects, THC produces euphoria, disinhibition, amnesia, anxiety/nervousness, ataxia, confusion, dizziness, hallucination, paranoid reaction, somnolence, nausea, vomiting, tachycardia, acute and chronic respiratory effects, and immunosuppression, as well as behavioral and cognitive impairment. [9,10] Dose dependent relationships between THC exposure and both tachycardia and hypertension have been reported. In a 2012 study, administration of oral THC to healthy individuals was associated with behavioral and physiological effects that include anxiety, dysphoria, positive psychotic symptoms, physical and mental sedation, subjective intoxication, and an increase in heart rate.[11] In another clinical study, the negative health effects associated with pure THC was demonstrated following its administration to healthy individuals under controlled conditions.[12] In this study, cannabidiol (CBD, a cannabinoid found with the marijuana plant) or placebo was administered ahead of intravenous THC to determine if CBD inhibited THC-elicited psychosis and cognitive impairment. The results demonstrated that subjects receiving CBD prior to THC exhibited less THC-paranoia and better episodic memory as compared to subjects receiving THC alone. The authors stated that these findings supported the idea that high-THC/low-CBD containing cannabis products are associated with increased risks for mental health problems.

The synthetic cannabinoids encountered on the illicit market are predominantly potent cannabinoid agonists that are pharmacologically similar to THC. Synthetic cannabinoids, like THC, bind to and activate the CB1 receptor, while producing euphoric and hallucinogenic effects. Currently, the term "synthetic cannabinoids" represents a group of substances with a

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[9] Proposed Rules, 81 Fed. Reg. 156 (August 12, 2016) (Docket No. DEA–427).
[10] Marinol (Dronabinol) NDA 18-651/S-021, Unimed Pharmaceuticals, Inc., www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf (2004).
[11] R. Martin-Santos, J.A. Crippa, A. Batalla, S. Bhattacharyya, Z. Atakan, S. Borgwardt, P. Allen, M. Seal, K. Langohr, M. Farre, AW. Zuardi & P.K. McGuire, *Acute Effects of a Single, Oral Dose of d9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) Administration in Healthy Volunteers*, 18 Current Pharmaceutical Design, 4966-79 (2012).
[12] A. Englund, P.D. Morrison, J. Nottage, D. Hague, F. Kane, S. Bonaccorso, J.M. Stone, A. Reichenberg, R. Brenneisen, D. Holt, A. Feilding, L. Walker, R.M. Murray & S. Kapur, *Cannabidiol Inhibits THC-elicited Paranoid Symptoms and Hippocampal-dependent Memory Impairment*, 27 Journal of Psychopharmacology, 19-27 (2013).

common pharmacological property: activation of the CB1 cannabinoid receptor. A "synthetic cannabinoid" should be defined as a substance that acts as an agonist at the CB1 receptor.

While no human studies have been conducted regarding these illicit synthetic cannabinoids, many case reports have documented the unintended consequences following the use of these toxic chemicals.[13,14,15,16] Serious bodily harm and adverse effects have occurred from the ingestion of synthetic cannabinoids. These have included seizures, cardiotoxicity, psychosis, agitation, multi-organ failure, central nervous system deficits and death amongst many others.

Patterns of abuse and harms associated with their abuse

The popularity of synthetic cannabinoids and their associated products has increased since January 2010, as evidenced by the increasing number of law enforcement seizures and public health and media reports. The Department of Health and Human Services, along with a recent study, have observed that synthetic cannabinoid abuse has been repeatedly noted in athletes, military personnel, employees who undergo frequent drug testing, and other individuals seeking intoxication while hoping to evade detection.[17] These substances and their products, commonly marketed as "legal highs" with a disclaimer of "not for human consumption," are routinely sold through venues including the internet or darkweb marketplaces, gas stations, convenience and corner stores.

Recent data originating from a multi-state outbreak involving synthetic cannabinoids demonstrated that while the predominant users of these products are between the ages of 18-34, users under the age of 12 years old and those up to and older than 65 are also abusing synthetic cannabinoid products.[18,19] A person with a smartphone and a form of currency can easily locate and discretely purchase any number of various products containing synthetic cannabinoids. Aside from the toxicity and bodily harm previously described, emergency responders are at a disadvantage because (given the proliferation of different synthetic cannabinoids) they often do not know what actual substance was ingested by the patient. And, the synthetic cannabinoids often do not appear on regular drug screens. Further compounding the problem is that adverse effects routinely render a patient either unconscious or in an agitated, psychotic and/or disoriented state so severe that the user is unable to communicate to a first responder what product was used. Additional information regarding the adverse health impacts of synthetic cannabinoids can be found in a statement the DEA provided to the Commission on March 15, 2017.[20]

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[13] M.D. Schwartz, et al. (2015).
[14] J. Trecki, et al. (2015).
[15] J.A. Tyndall, et al. (2015).
[16] A.J. Adams, et al. (2017).
[17] E.E. Bonar, et al., (2014).
[18] J. Trecki, et al. (2015).
[19] 64 Morbidity Mortality Weekly Report, 1121-2 (2015).
[20] Statement of Dr. Terry Boos & Shontal Linder, Hearing on Sentencing Policy for Synthetic Drugs at 23-24 (March 15, 2017), https://www.ussc.gov/sites/default/files/pdf/amendment-process/public-hearings-and-meetings/20170418/DEA.pdf.

Potency of Synthetic Cannabinoids

Thirty-eight synthetic cannabinoids are currently listed in Schedule I of the CSA. In combination with the serious adverse effects observed by law enforcement and the increasing number of case reports and autopsies being published by doctors and medical examiners regarding synthetic cannabinoids, it would be inappropriate to conduct controlled human studies with a drug absent a medical benefit only to determine its potency. However, to date, animal drug discrimination studies have been conducted on a large number of synthetic cannabinoids to evaluate the efficacy of these substances and to determine their relative potency to humans. According to these studies, all synthetic cannabinoids tested fully shared discriminative stimulus effects of THC in drug discrimination studies. Animal discriminative effects are believed to parallel subjective effects in humans.[21, 22]

Regarding potency, drug discrimination data are available on at least 26 different synthetic cannabinoids. JWH-018, a synthetic cannabinoid, was shown in the drug discrimination assay to be approximately 3 times as potent as THC, while AM2201, another synthetic cannabinoid, was shown to be approximately 5 times as potent as THC using the same assay.[23] Newer synthetic cannabinoids have been shown to be even more potent than either JWH-018 or AM2201.[24,25] On rare occasions, synthetic cannabinoids have been shown to be less potent in the drug discrimination assay than THC. We have observed that substances with a lower potency are often abandoned by manufacturers following negative user reports relating to their pharmacological effects.[26] And, just as with cathinones, because potency compares the amounts of drugs that produce the same or similar effect, users can simply adjust the dose of a given drug to achieve the desired effects. Therefore, it is not advisable to use the pharmacological potency of the drug as the sole factor in determining the marijuana equivalency. Other factors, such as toxicity and risks of adverse impacts on public health, should also be considered. Again, as in the case of cathinones, the equivalency for the class of cannabinoids should reflect the fact that all of the substances in the class were, and will be, synthesized and trafficked to evade our legal system.

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[21] R.L. Balster, *Drug abuse potential evaluation in animals*, 86 British Journal of Addiction, 1549-158 (1991).
[22] L.H. Brauer, A.J. Goudie & H. de Wit, *Dopamine ligands and the stimulus effects of amphetamine: animal models versus human laboratory data,* 130 Psychopharmacology (Berl), 2-13 (1997).
[23] M.B. Gatch & M.J. Forster, *Δ9-Tetrahydrocannabinol-like discriminative stimulus effects of compounds commonly found in K2/Spice*, 25 Behavioural Pharmacology, 750-757 (2014).
[24] M.B. Gatch & M.J. Forster, *Δ9-Tetrahydrocannabinol-like effects of novel synthetic cannabinoids found on the gray market*, 26 Behavioural Pharmacology, 460-468 (2015).
M.B. Gatch & M.J. Forster, *Δ9-Tetrahydrocannabinol-like effects of novel synthetic cannabinoids in mice and rats*, 233 Psychopharmacology, 0901-1910 (2016).
[26] J.L. Wiley, J.A. Marusich, T.W. Lefever, K.R. Antonazzo, M.T. Wallgren, R.A. Cortes, P.R. Patel, M. Grabenauer, K.N. Moore & B.F. Thomas, *AB-CHMINACA, AB-PINACA, and FUBIMINA: Affinity and Potency of Novel Synthetic Cannabinoids in Producing Δ9-Tetrahydrocannabinol-Like Effects in Mice*, 354 Journal of Pharmacology and Experimental Therapeutics, 328-39 (2015).

Patterns of trafficking and harms associated with their trafficking

Synthetic cannabinoids are predominantly produced in Chinese laboratories. They are then shipped in powder form through freight forwarding companies before ending up in the United States. The powder is then commonly dissolved in a liquid and applied to leafy plant material that resembles marijuana. The finished product is packaged in multiple forms that can include rolling into cigarettes or joints, sold in non-descript plastic baggies, or most commonly inserted into a foil packaging, adorned with colorful cartoon characters or other pictures that attempt to distinguish brand and seller identity. They are often sold using names such as "Spice" and "K2." These various products are then distributed to retail outlets or can be sold directly to users through various mail services via internet websites. The law enforcement encounters of synthetic cannabinoids in the United States have increased dramatically in recent years. For example, according to the DEA National Forensic Laboratory Information System (NFLIS), law enforcement encounters of substances identified as synthetic cannabinoids by federal, state, and local forensic laboratories increased from 23 reports in 2009 to 37,500 reports in 2014.[27] Since 2011, NFLIS has received over 200,000 reports of synthetic cannabinoids.

New synthetic cannabinoids are rapidly introduced on the illicit market in response to domestic and international drug controls. These products containing synthetic cannabinoids often do not bear accurate labeling information regarding ingredients or the health risks and potential hazards associated with these products. This lack of information poses significant risks to users who may not know what they are purchasing or the risk associated with the abuse of those products. With no regard for the user, these products are being distributed with no quality assurance and deceptive labeling practices. The variation of substance(s) encountered in designer drug products creates numerous challenges for public health and law enforcement. Synthetic cannabinoids continue to demonstrate serious adverse effects across age brackets that greatly surpass those observed with THC, are frequently marketed to and abused by those of a young age. These substances continue to be a threat to public safety, continue to be illegally imported into the United States, and are mixed with plant material to produce a large number of doses per gram.

Analysis of two synthetic cannabinoid products labeled as "Scooby Snax" encountered within a few months of each other were found to have different contents (Fig. 2 and 3), while some packets contain mixtures of various synthetic cannabinoids (Fig. 4).

[27] Statement of Chuck Rosenberg, Acting DEA Administrator before the Senate Judiciary Committee at 2 (June 7, 2016), https://www.judiciary.senate.gov/imo/media/doc/06-07-16%20Rosenberg%20Testimony.pdf.

Fig. 2 – UR-144

Fig. 3 – PB-22

Fig. 4 – UR-144 and XLR11

New variations of synthetic cannabinoid products continue to be encountered, including hookah pens and electronic cigarettes that are becoming more popular (Fig. 5, 6 and 7).

Fig 5. – AB-CHMINACA

Fig 6. AB-FUBINACA & AB-PINACA

Fig. 7. AB-FUBINACA

Summary

Synthetic cannabinoids represent a group of pharmacologically similar substances that are commonly abused by a wide group of individuals with often serious and toxic consequences. Manufactured from templates published by legitimate scientists and chemically manipulated in the attempt to avoid law enforcement and prosecution, synthetic cannabinoids will continue to evolve and remain a drug of choice for those hoping to avoid detection of their drug abuse.

Pharmacological data demonstrate that synthetic cannabinoids are agonists at the CB1 receptor, resulting in a psychoactive experience along with a multitude of adverse effects.

The advantage to a class approach for synthetic cannabinoids would be to offer clarity and consistency and promote judicial economy. Creating an equivalency for the class would also provide defendants with notice of the sentence they face, and it would serve to simplify the guidelines.

These data demonstrate synthetic cannabinoids pose a significant risk to the user and remain a challenge for communities. The DEA is hopeful that the Commission adopts a class approach to synthetic cannabinoids.