U.S. Department of Justice

Drug Enforcement Administration

Schedules of Controlled Substances: Placement of [1-(5-Fluoropentyl)-1*H*-indazol-3-yl](naphthalen-1-yl)methanone (THJ-2201), *N*-1-Amino-3-methyl-1-oxo-2-butanyl]-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA), and *N*-[1-Amino-3-methyl-1-oxo-2-butanyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA) into Schedule I

Background, Data, and Analysis:

Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b)

Prepared by

Diversion Control Division, Drug and Chemical Evaluation Section

Washington, D.C. 20537

January 2017

I. Background

On January 30, 2015, the Administrator of the Drug Enforcement Administration (DEA) published a Final Order in the *Federal Register* (80 FR 5042) temporarily placing three synthetic cannabinoid (SC) substances in schedule I of the Controlled Substances Act (CSA) upon finding that these substances pose an imminent threat to public safety. The three SCs temporarily controlled under the CSA are *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA), N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA) and [1-(5-fluoropentyl)-1*H*-indazol-3-yl](naphthalen-1-yl)methanone (THJ-2201). These three SCs have not been investigated for medical use nor are they intended for human use. With no known legitimate use and safety information, manufacturers are surreptitiously adulterating plant material with these SCs and distributors are selling the associated products which pose potentially dangerous consequences to the consumer. The adulterated products, such as "Spice", "K2" and many others, are marketed under the guise of "herbal incense" or "potpourri" products and as "legal alternatives to marijuana" or "legal high". Data from law enforcement, health care practitioners, and scientific and medical literature indicate that these products are being abused for their psychoactive properties in the absence of information regarding their safety. There have been reports of admissions to hospital emergency departments (ED) or death following abuse of these three synthetic cannabinoids.

In their scientific and medical evaluation, the Department of Health and Human Services (HHS) stated that since the first detection of JWH-018 in 2008 (Jaenicke et al., 2014), scientific publications have mentioned encounters of over 500 various SCs on the illicit market. HHS also noted that because the composition of SC-containing products continues to evolve over time; often consumers have limited knowledge as to the actual content or amount of SC applied, placing the user at risk.

As described in the January 30, 2015 Final Order, AB-CHMINACA, AB-PINACA and THJ-2201 are SCs that are pharmacologically similar to delta-9-tetrahydrocannabinol (Δ^9-THC), the principal psychoactive chemical in marijuana, and to schedule I SCs such as JWH-018, AM2201, ADB-PINACA and AB-FUBINACA. The Assistant Secretary of Health for the HHS has advised that there are no exemptions or approvals in effect for AB-CHMINACA, AB-PINACA and THJ-2201 under section 505 (21 U.S.C. 355) of the Federal Food, Drug, and

Cosmetic Act. As stated by the HHS, AB-CHMINACA, AB-PINACA and THJ-2201 have no known accepted medical use. They are not the subject of any approved new drug applications (NDAs) or investigational new drug applications (INDs), and are not currently marketed as approved drug products.

The Food and Drug Administration (FDA) recommended that [1-(5-fluoropentyl)-1*H*-indazol-3 -yl](naphthalen-1-yl)methanone (THJ-2201), *N*-1-amino-3-methyl-1-oxo-2-butanyl]-1-pentyl-1*H*-indazole-3-carboxamide, (AB-PINACA), and *N*-1-amino-3-methyl-1-oxo-2-butanyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA) and their salts be placed in Schedule I of the Controlled Substances Act (CSA).

II. Eight Factors Determinative of Control

In accordance with the provisions of 21 U.S.C. 811(b) of the Controlled Substances Act (CSA), the DEA has gathered the necessary data, including scientific, public health, and law enforcement information on these three substances, as well as their associated products. The DEA collected data in light of the information to be considered under 21 U.S.C. 811(c). On August 26, 2015, the DEA requested from the Assistant Secretary of Health for HHS a scientific and medical evaluation and scheduling recommendation for AB-CHMINACA, AB-PINACA and THJ-2201 pursuant to 21 U.S.C. 811(b). Administrative responsibilities for evaluating a substance for control under the CSA are performed for the HHS by the FDA, with the concurrence of the National Institute on Drug Abuse (NIDA) ((Memorandum of Understanding, 50 FR 9518–20) (Mar. 8, 1985)). Upon receipt and evaluation of the scientific and medical evaluation and scheduling recommendation from the Assistant Secretary on November 15, 2016, the DEA reviewed these documents and all other relevant data and conducted its own eight-factor analysis on these SCs pursuant to 21 U.S.C. 811(c). The DEA's eight-factor review as presented below finds that AB-CHMINACA, AB-PINACA and THJ-2201, and their salts, isomers, and salts of isomers warrant control in schedule I of the CSA.

Factor 1: The Actual or Relative Potential for Abuse

In addition to the information the HHS provided in its scientific and medical evaluation document for AB-CHMINACA, AB-PINACA and THJ-2201 (HHS review, 2016), the DEA

considers all other relevant data regarding the actual or relative potential for abuse. The first factor the DEA must consider is the actual or relative potential for abuse of AB-CHMINACA, AB-PINACA and THJ-2201. The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests that the DEA consider the following criteria in determining whether a particular drug or substance has a potential for abuse:[1]

a) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or

b) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or

c) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or

d) The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

a. There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

Through epidemiological and case report data, HHS has demonstrated that the ingestion of AB-CHMINACA, AB-PINACA and/or THJ-2201 in sufficient amounts is creating a hazard to the health and safety of both the individual users and others within the community. Adverse effects observed following the ingestion of SCs, including AB-CHMINACA, AB-PINACA and THJ-2201, include nausea and vomiting, shortness of breath or depressed breathing,

[1] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); reprinted in 1970 U.S.C.C.A.N. 4566, 4603.

hypertension, tachycardia, chest pain, muscle twitching, acute renal failure, anxiety, agitation, psychosis, suicidal ideation, and cognitive impairment (Castaneto et al., 2014; Trecki et al., 2015; Tyndall et al., 2015). HHS also stated that SCs like AB-CHMINACA, AB-PINACA and THJ-2201 are easily accessible and difficult to detect in standard urine drug screens, which contributes to their popularity and high rates of abuse (Auwarter et al., 2009).

The American Association of Poison Control Centers[2] (AAPCC) reported 7,779 calls to poison centers about exposures to SCs from January 1, 2015 through December 31, 2015. This number is significantly higher than the number of calls in all of 2014 (3,682), or all of 2013 (2,668). In 2015, there was a notable increase in calls during April (1,512) and May (1,205), falling to a stable, but higher baseline for the rest of the year: a seasonal pattern not seen in previous years. In 2016, the numbers of exposure calls (2,695) have dropped again, mirroring those of 2013 (2,668). Although the AAPCC does not identify specific cannabinoid substances, their data do support the high prevalence of toxic exposures to SCs in general. In 2015, at least 15 calls to Poison Centers regarding SCs exposures were associated with deaths, which is triple the 5 deaths associated with such calls for all of 2014.

b. There is significant diversion of the drug or substance from legitimate drug channels.

The HHS stated that there are no FDA-approved drug products containing AB-CHMINACA, AB-PINACA and THJ-2201 in the United States and there appear to be no legitimate sources for these substances as marketed drugs. Therefore this criterion for assessing abuse potential of these SCs is not applicable.

[2] The American Association of Poison Control Centers collects information logged by the numerous regional Poison Control Centers (PCCs). Records are from self-reported calls; therefore, they reflect only information provided when the public or healthcare professional reports an actual or potential exposure to a substance (e.g. an ingestion, inhalation, or topical exposure), or requests informational material. It warrants noting that these exposures do not inherently represent an instance of poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance. The AAPCC indicated that a significant proportion of the reports were generated from hospital emergency departments or en-route to a medical treatment facility.

c. *Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.*

According to the HHS, because AB-CHMINACA, AB-PINACA and THJ-2201 are not approved for medical use and are not formulated or available for clinical use, the human use of these substances is assumed to be on an individual's own initiative, rather than on the basis of medical advice from a practitioner licensed by law to administer drugs. Further, published scientific and medical literature (Schwartz et al, 2014; Trecki et al, 2015; Tyndall et al., 2015), and reports from AAPCC and law enforcement reports indicate that individuals are taking these SCs on their own initiative, rather than on the basis of medical advice of a licensed practitioner.

d. The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that they will have the same potentiality for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

As noted by the HHS, pharmacological studies sponsored by NIDA have demonstrated that AB-CHMINACA, AB-PINACA and THJ-2201 are similar to other schedule I SCs. All three of these substances, similar to schedule I SCs, display high affinity binding and potent agonist functional activity at the cannabinoid (CB1) receptor, while drug discrimination studies have demonstrated the ability of all three substances to substitute for Δ^9-tetrahydrocannabinol (Δ^9-THC) (see factor 2). The HHS stated in their review that AB-CHMINACA, AB-PINACA and THJ-2201 are markedly more potent at CB1 receptors than the natural phytocannabinoids (cannabinoids that occur naturally in the cannabis plant, i.e. Δ^9- THC).

Factor 2: Scientific Evidence of Pharmacological Effect, if Known

In vitro receptor binding and functional assays were conducted with AB-CHMINACA, AB-PINACA and THJ-2201. In addition, drug discrimination assays using Sprague Dawley rats

were performed to identify drugs with similar subjective effects to Δ^9-THC. The tetrad assay was also conducted for AB-CHMINACA and AB-PINACA. The results are shown in Tables 1 and 2. These results indicate that AB-CHMINACA, AB-PINACA and THJ-2201, similar to other schedule I SCs, bind to CB1 receptors with high affinity and act as agonists at CB1 receptors.

Table 1. *In vitro* binding and functional and *in vivo* drug discrimination data for AB-CHMINACA, AB-PINACA and THJ-2201

	In vitro		***In vivo***
	Binding at CB1[3]	**Function at CB1**[4]	**Drug Discrimination**[5]
AB-CHMINACA	K_i = 0.78 nM[a]	EC_{50} = 7.4 nM[a]	Full substitution (ED_{50} = 0.34 µmol /kg[c])
AB-PINACA	K_i = 2.87 nM[c]	EC_{50} = 71 nM[c]	Full substitution (ED_{50} = 3.78 µmol /kg[c])
THJ-2201	K_i = 5.7 nM[b]	EC_{50} = 0.6 nM[b]	Full substitution (ED_{50} = 0.15 mg/kg[d])
[a] Aung et al. 2000; [b] NIDA, 2014a, 2015 [c] Wiley et al., 2015; [d] NIDA, 2014b			

Table 2. Tetrad data of AB-PINACA and AB-CHMINACA‡ (ED50 (μmol/kg))[a]

	SA[b]	**MPE[c]**	**RT[d]**	**RI[e]**
Δ^9-THC	104 (51-216)	34 (20-58)	30 (23-39)	30 (17-53)
AB-PINACA	7.6 (3.3-17.4)	13.7 (5.5-34.2)	5.3 (3.5-8.0)	13.9 (6.8-28.4)
AB-CHMINACA	1.8 (0.7-4.5)	2.0 (1.3-3.0)	1.1 (0.7-1.6)	2.7 (1.9-3.9)
[a] Wiley et al., 2015; [b] SA - percentage of inhibition of spontaneous activity; [c] MPE -				

[3] In vitro CB1 receptor binding assays are conducted in membrane preparations from HEK-293 cells or CHO cells that expressed human CB1 receptors with [^{3}H]CP 55940 as a radioligand.

[4] In vitro CB1 receptor functional assays for these substances with the exception of ADB-PINACA are conducted by measuring morphological responses following drug administration in CHO cells that expressed human CB1 receptors. For determination of agonist functional activity of ADB-PINACA, cAMP inhibition assay was conducted using CHO cells that expressed human CB1 receptors.

[5] Discriminative stimulus effects are evaluated by the ability of a test drug to substitute for the discriminative stimulus effects of Δ^9-THC (3 mg/kg) in rats.

percentage of maximum possible effect in tail flick test; [d] RT - change in rectal temperature in °C; [e] RI - ring immobility; [‡] Values in parenthesis represent ± 95% confidence intervals

The drug discrimination assay is a well-accepted animal model used to predict subjective effects of substances in humans (Schuster and Johanson, 1988; Balster and Bigelow, 2003; Tai et al., 2014). In NIDA-sponsored drug discrimination studies, AB-CHMINACA, AB-PINACA and THJ-2201, similar to other schedule I SCs (e.g., JWH-018; AM2201; ADB-PINACA, AB-FUBINACA etc.), fully substituted for Δ^9-THC in animals trained to discriminate the stimulus effects of Δ^9-THC (3 mg/kg) from its vehicle control. Based on results from the receptor binding (Ki), CB1 functional assay, and drug discrimination studies, the HHS concluded that AB-CHMINACA, AB-PINACA and THJ-2201act as full psychoactive cannabinoid agonists with no antagonist activity, and that these three substances are more potent than Δ^9-THC (schedule I), and are similar in activity to JWH-018, AM2201, ADB-PINACA, and AB-FUBINACA (schedule I). As stated by the HHS, these data indicate that AB-CHMINACA, AB-PINACA and THJ-2201 are more potent than schedule I cannabinoid Δ^9-THC in producing behavioral pharmacological effects and share pharmacological effects with other synthetic cannabinoids in schedule I, such as JWH-018.

Human Studies

No human studies involving AB-CHMINACA, AB-PINACA and THJ-2201 have been reported.

Factor 3: The State of Current Scientific Knowledge Regarding AB-CHMINACA, AB-PINACA and THJ-2201

The HHS stated that AB-CHMINACA, AB-PINACA and THJ-2201 are all potent cannabinoid agonists that are pharmacologically similar to Δ^9-THC. Emerging in the early 1980's, SCs were originally designed to investigate structure activity relationships (SAR) based on the potent substance, 9-nor-9β-hydroxyhexahydrocannabinol (HHC) (Weissman et al., 1982; Melvin et al., 1984). Interest in various structural classes was generated by the mouse vas

deferens (MVD) and prostaglandin synthetase activity of pravadoline and subsequent finding of its affinity to the cannabinoid receptor (Huffman, 2009).

Chemistry and Physical Properties

Figure 1. Chemical Structures of AB-CHMINACA, AB-PINACA and THJ-2201

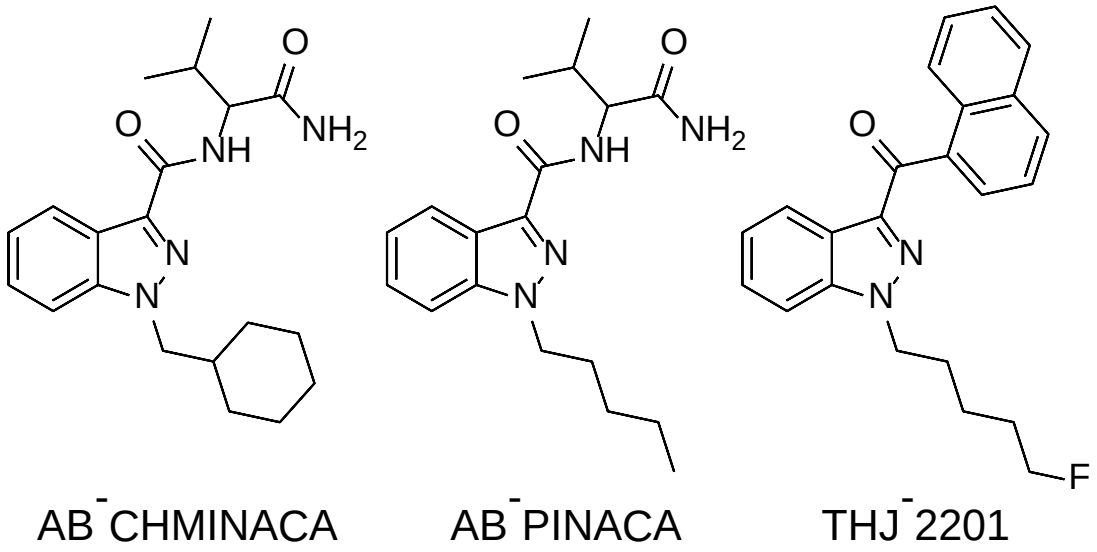

Table 3. The chemical and physical properties of *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide

Synonyms	**AB-CHMINACA**
Systemic Name (IUPAC, CAS)	***N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide**
CAS #	**1185887-21-1**
Chemical Formula	**$C_{20}H_{28}N_4O_2$**
Molecular Weight	**356.46 g mol^{-1}**

Table 4. The chemical and physical properties of *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide

Synonyms	**AB-PINACA**
Systemic Name (IUPAC, CAS)	***N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide**
CAS #	**1445752-09-9**
Chemical Formula	**$C_{18}H_{26}N_4O_2$**
Molecular Weight	**330.43 g mol^{-1}**

Table 5. The chemical and physical properties of [1-(5-fluoropentyl)-1*H*-indazol-3-yl](naphthalen-1-yl)methanone

Synonyms	**THJ-2201, AM(N)-2201, AM2201 indazole, 5-fluoropentyl JWH-018 indazole analog, 5-fluoro THJ-018**
Systemic Name (IUPAC, CAS)	**[1-(5-fluoropentyl)-1*H*-indazol-3-yl](naphthalen-1-yl)methanone**
CAS #	**1801552-01-1**
Chemical Formula	**$C_{23}H_{21}FN_2O$**
Molecular Weight	**360.42g mol^{-1}**

<u>*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA)</u>

AB-CHMINACA shares structural features with schedule I substances such as AB-FUBINACA and AKB48 . AB-CHMINACA, AB-FUBINACA, and AKB48 all have the indazole ring as a core structure with substitutions at 1- and 3-positions. All three substances are substituted at the 3-position with a carbonyl linker and an additional nitrogen atom collectively known as an amide. AB-CHMINACA and AB-FUBINACA are further substituted at the amide nitrogen atom with the 1-amino-3-methyl-1-oxobutan-2-yl group. The 1-position of the core indazole ring system in AB-CHMINACA and AB-FUBINACA is substituted with a cyclohexylmethyl and 4-fluorobenzyl group, respectively.

<u>*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA)</u>

AB-PINACA is also based on the same indazole core structure as AB-CHMINACA, AB-FUBINACA, and AKB48, with substitutions at 1- and 3-positions of the indazole ring. All four of these substances are substituted at the 3-position with an amide. Similar to AB-CHMINACA and AB-FUBINACA, AB-PINACA is substituted at the amide nitrogen atom with the 1-amino-3-methyl-1-oxobutan-2-yl group. AB-PINACA, like AKB48, contains a pentyl group on the indazole 1-position.

[1-(5-fluoropentyl)-1*H*-indazol-3-yl](naphthalen-1-yl)methanone (THJ-2201)

THJ-2201 is also based on the same indazole core structure as AB-PINACA, AB-CHMINACA, AB-FUBINACA, and AKB48 with substitutions at the 1- and 3-positions of the indazole ring. These substitutions for THJ-2201 are the same substitutions as are found in AM-2201 with indole as the core structure. This single atom substitution from indole to indazole is the only difference between AM2201 and THJ-2201. AM2201 and THJ-2201 are both substituted at the 3-position with a carbonyl group known as a ketone. The ketone groups of both substances are further substituted with a naphthyl group. The 1-position of core structures of THJ-2201 and AM2201 are substituted with a fluorinated alkyl group, known as a 5-fluoropentyl group (Huffman et al., 1994; Wiley et al., 1998; Aung et al., 2000; Manera et al., 2008; Huffman, 2009; Shevyrin et al., 2014).

Chemical synthesis

According to HHS, AB-PINACA and AB-CHMINACA were first synthesized in 2009. The procedure for synthesis of AB-PINACA was published in 2015 (Banister et al., 2015), while the synthetic procedures for THJ-2201 and AB-CHMINACA are not published in the scientific literature. However the presence of THJ-2201 and AB-CHMINACA in the illegal market suggests that synthetic procedures for these SCs have been determined.

Metabolism and Pharmacokinetics

Takayama et al. (2014) analyzed the metabolites of AB-PINACA using a method based upon the oxidation by cytochrome p450 superfamily enzymes in the microsomes in human liver cells. This method mimics the first oxidation reaction in metabolism by cytochrome p450 enzymes in humans. The oxidation of AB-PINACA seemed to occur on the 1-pentyl moiety. Interestingly, of the three metabolites identified (one major and two minor metabolites), one of the minor metabolites seemed to be similar to those found for both ADB-FUBINACA and AB-FUBINACA, while the remaining two metabolites (one major and one minor) were suggested to vary from the metabolites for ADB-FUBINACA and AB-FUBINACA (Takayama et al., 2014).

Thomsen et al. (2014) also analyzed the metabolites of AB-PINACA using human liver microsomes. Results demonstrated that a major metabolic pathway for AB-PINACA was the enzymatic hydrolysis of the primary amide by carboxylesterase 1 (CES1) [a major human

hepatic and pulmonary enzyme], resulting in the major metabolite AB-PINACA-COOH, and mono-hydroxylation of the N-pentyl chain in AB-PINACA, yielding another major metabolite. In all, 10 metabolites of AB-PINACA were identified.

Scheidweiler et al. (2015) developed and validated a liquid chromatography quadrupole/time-of flight MS (LC-QTOF MS) urine method for identifying metabolites for synthetic cannabinoids, including for AB-PINACA. Results demonstrated two different metabolites of AB-PINACA including AB-PINACA N-hydroxypentyl and AB-PINACA pentanoic acid metabolites, both with limits of detection in urine of 5 µg/L (Scheidweiler et al., 2015).

Diao et al. (2016) identified 27 metabolites for THJ-2201 using human hepatocytes via high resolution mass spectrometry. Products of oxidative defluorination plus subsequent carboxylation or glucuronidation, and glucuronidation of hydroxylated metabolites for THJ-2201 were observed.

Wohlfarth and his associates (2015) incubated urine samples in liver microsomes and identified 23 different metabolites of AB-PINACA. They found that the most abundant metabolites were the result of several reactions which included: carboxamide hydrolysis, hydroxylation, ketone formation, carboxylation, epoxide formation with subsequent hydrolysis, or combinations of these reactions. These resulted in three major metabolites; AB-PINACA carboxylic acid, carbonyl-AB-PINACA, and hydroxypentyl AB-PINACA (Wohlfarth et al., 2015).

These results and others are described in Table 6.

Table 6. Metabolism and pharmacokinetics using cell assay

Substance	**Pathways Observed/ Common Metabolite Observed**	**# of Metabolites Observed**	**Assay Conditions**	**Citation**
CELL ASSAYS				
THJ-2201	Oxidative defluorination plus subsequent carboxylation or	27	Cryopreserved human hepatocytes	Diao et al. (2016)

	glucuronidation, and glucuronidation of hydroxylated metabolites			
AB-PINACA	Oxidation by cytochrome p450	3	Human liver microsomes	Takayama et al. (2014)
AB-PINACA	Enzymatic hydrolysis of the primary amide by carboxylesterase 1 (CES1)	10	Human liver microsomes	Thomsen et al. (2014)
AB-PINACA	Carboxamide hydrolysis, hydroxylation, ketone formation, carboxylation, epoxide formation with subsequent hydrolysis, or combinations of these reactions	23	Human liver microsomes	(Wohlfarth et al., 2015)
AB-CHMINACA	Degradation by cytochrome P450 enzymes	26	Human liver microsomes	Erratico et al. (2015); Wurita et al. (2016)
BIOLOGICAL SAMPLES				
AB-PINACA	Liquid chromatography quadrupole/time-of flight MS (LC-QTOF MS)		Urine samples	Scheidweiler et al. (2015)
AB-CHMINACA	Hydroxylation of the cyclohexyl ring,		Urine, plasma, and serum of	Tyndall et al. (2015)

	hydrolysis of the terminal amide, hydrolysis of the internal amide, and hydroxylation/oxidation of the isopropyl group		emergency room patients who consumed synthetic cannabinoids	

Medical Application

A letter dated September 17, 2014 was sent from the DEA Deputy Administrator to the Assistant Secretary for Health, of the Department for Health and Human Services as notification of intent to temporarily place these three substances in schedule I and solicited comments, including whether an exemption or approval was in effect for the substances in question under the Federal Food, Drug, and Cosmetic Act. The Assistant Secretary of Health responded that there were no current INDs or NDAs for these synthetic cannabinoids in a letter to the DEA Deputy Administrator dated September 30, 2014. The HHS in its scientific and medical evaluation and scheduling recommendation dated November 14, 2016, reiterated that these three SCs are not the subjects of any approved NDAs or INDs; are not currently marketed as approved drug products; and have no accepted medical uses in the United States.

Factor 4: Its History and Current Pattern of Abuse

SCs have been developed over the last 30 years as tools for investigating the cannabinoid system (Weissman et al., 1982; Huffman et al., 1996; Huffman et al., 1999). Synthetic cannabinoids intended for illicit use were first encountered in the United States in November 2008 during seizure and analysis by the United States Customs and Border Protection (CBP) of a shipment of "Spice" in Dayton, Ohio. Additionally at approximately the same time, in December 2008, JWH-018 and cannabicyclohexanol (CP-47,497 C8 homologue) were identified by German forensic laboratories. Since the initial identification of JWH-018 (November 2008), many other SCs have been found applied on plant material and encountered as designer drug products (Auwarter et al., 2009; DEA, 2009; DEA, 2012; DEA, 2013; DEA, 2014). The popularity of these

cannabinoids and their associated products has increased since January 2010 in the United States as evidenced by the increasing number of seizures and public health and media reports. (See Factor 5).

The HHS noted that SC 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. (Seely et al., 2012; CDC, 2013a,b; Schwartz et al., 2015).

Numerous SCs have been identified as product adulterants, and law enforcement has seized bulk powder of these substances. Some initial SCs identified as being abused included JWH-018, JWH-073, JWH-200, CP-47,497, and CP-47,497 C8 homologue, followed shortly thereafter by new generations of SCs including drugs such as UR-144, XLR11, AKB48, PB-22, 5F-PB-22, AB-FUBINACA, ADB-PINACA and numerous other SCs varying only by slight modifications to their chemical structure. JWH-018, JWH-073, JWH-200, CP-47,497, and CP-47,497 C8 homologue were temporarily scheduled on March 1, 2011 (76 FR 11075), and later permanently placed in schedule I by section 1152 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144) on July 9, 2012. Section 1152 of FDASIA amended the CSA by placing cannabimimetic agents and 26 specific substances (including 15 synthetic cannabinoids, 2 synthetic cathinones, and 9 synthetic phenethylamines of the 2C- series) into schedule I. UR-144, XLR11, and AKB48 were temporarily scheduled on May 16, 2013 (78 FR 28735). PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA were temporarily scheduled on February 10, 2014 (79 FR 7577) (Table 7).

AB-CHMINACA, AB-PINACA and THJ-2201 are another generation of SCs encountered by law enforcement. These substances and their products are commonly marketed as “legal highs” with a disclaimer of “not for human consumption.” As detailed in reports, law enforcement and public health officials are encountering the abuse of these substances (See Factor 5; Appendix 1) (CDC, 2013a, 2013b, 2013c; NFLIS, 2016 STRIDE, 2014; STARLiMS, 2016).

Table 7. Control actions and placement into Schedule I of the Controlled Substances Act (CSA)

Substances	Date of Temporary Control	Date of Permanent Control
JWH-018, JWH-073, JWH-200, CP-47,497, CP-47,497 C8 homologue	March 1, 2011 (76 FR 11075)	July 9, 2012 (section 1152 of FDASIA)
UR-144, XLR11, AKB48	May 16, 2013	May 11, 2016

	(78 FR 28735)	(81 FR 29142)
PB-22, 5F-PB-22, AB-FUBINACA, ADB-PINACA	February 10, 2014 (79 FR 7577)	September 6, 2016 (81 FR 61130)
AB-CHMINACA, AB-PINACA, THJ-2201	January 30, 2015 (80 FR 5042)	Current Scheduling Action

Numerous herbal incense products have been found to contain one or more SC(s) laced on plant material (NFLIS, 2016). Research and clinical reports have demonstrated that SCs are applied onto plant material so that the material may be smoked as users attempt to obtain "high," similar to marijuana (McKeever et al., 2015; Bonar et al., 2014). Data gathered from published studies (McKeever et al., 2015; Bonar et al., 2014), supplemented by discussions on Internet discussion websites and communications to DEA from law enforcement and public health demonstrate that these products are being abused mainly by smoking for their psychoactive properties and are marketed as "legal" alternatives to marijuana.

To lace the plant material, the SCs are generally dissolved in a solvent and sprayed on the plant material or the plant material is soaked in a solution of the dissolved substance (Vardakou et al., 2010; Wells and Ott, 2011). The majority of the SCs encountered on the illicit market have not been tested beyond preliminary pre-clinical laboratory screens before clandestine operators applied them on plant material (Lewin et al., 2014). The psychoactive properties are directly linked to the SCs laced on the plant material sold as retail products (Auwarter et al., 2009; EMCDDA, 2009; Atwood et al., 2010). Furthermore, Ogata et al. (2013) analyzed various herbal products and reported that the green plant material found in SC products was devoid of psychoactive effects demonstrating that the effects observed following ingestion of these products originate from the actual SC, and not the plant material.

A major concern of public health officials and medical professionals remains the targeting and direct marketing of SCs and SC-containing products to adolescents and youth (Auwarter et al., 2009; EMCDDA, 2009; Lindigkeit et al., 2009; Dresen et al., 2010; Hudson et al., 2010; Uchiyama et al., 2010; Uchiyama, 2012a; Uchiyama et al., 2012b; Oluwabasi et al., 2012; Durand et al., 2013; ONDCP, 2014). This is supported by law enforcement encounters and reports from emergency rooms (SAMHSA, 2012; Fattore and Fratta, 2011; Vandrey et al., 2012); however, abuse of these substances and related products by all age groups have been reported (Trecki et al., 2015). In 2010, an estimated 11,406 emergency department (ED) visits in the United States

involved a SC product (SAMHSA, 2012). In 2011, the estimated ED visits involving SCs increased significantly to an estimated 28,531 visits (SAMHSA, 2014) and 79% of these ED patients were between the ages of 12 and 29. In addition, the majority (65%) of these ED visits of patients aged 20 and younger did not involve any other substance. Of the remaining 35% of these individuals, the most frequently abused substances in combination with SCs were marijuana (17%), pharmaceuticals (16%) and alcohol (15%) (SAMHSA, 2014). Individuals, including minors, are purchasing SCs from Internet websites, gas stations, convenience stores, and head shops. Reports from clinicians and law enforcement personnel have documented overdoses in juveniles as low as 13 and 14 years old (see Factor 6). In addition, an infant with confirmed exposure to SC was admitted to the intensive care unit following ingestion of a SC-containing product (see Factor 6).

Two research articles propose that the packaging is professional and inconspicuous (unlabeled as to the drug contained within), targeting young people, possibly eager to use cannabis, but who are afraid of the judicial consequences and/or association with illicit drugs (Lindigkeit et al., 2009; Schifano, 2009). In addition, a 2014 survey of patients seeking substance abuse disorder treatment reported multiple motives for use of SCs. The most common motives included curiosity (91%), feeling good/getting high (89%), relaxation (71%), and getting high without having a positive drug test (71%). Demographically, those with lifetime SC use were significantly younger than respondents who abused drugs other than SCs (Bonar et al., 2014). These data coincide with U.S. Drug Courts[6] that have communicated concerns related to the abuse of SCs and a response rate of greater than 30% by juveniles subject to routine drug screens from a sampling (information communicated to the DEA).

According to the Monitoring the Future (MTF) Report for 2015, the annual prevalence rates for use of SCs, colloquially referred to as 'synthetic marijuana', in 8th and 10th graders were 4.4% and 8.8%, respectively in 2012. MTF reported an annual prevalence of use of SCs of 11.4% in twelfth graders. Twelfth grade prevalence remained relatively constant in 2012, at 11.3%. Use in the 8th, 10th, and 12th grades dropped in 2013, and the decline was significant among 12th

[6] Drug courts were developed to achieve a reduction in recidivism and substance abuse among nonviolent, substance abusing offenders by increasing their likelihood for successful rehabilitation through early, continuous, and intense judicially supervised treatment, mandatory periodic drug testing, and the use of appropriate sanctions and other rehabilitation services. Drug courts analyze specimens from participants for new and existing drugs of abuse.

graders. According to MTF report for 2016, the declines continued in 2014 and were significant for 10th and 12th graders. In 2014, the annual prevalence's for 8th, 10th, and 12th graders were 3.3%, 5.4%, and 5.8%, respectively (Johnston et al., 2015). In 2015, the annual prevalence's for 8th, 10th, and 12th graders were 3.1%, 4.3%, and 5.2%. In 2016, the annual prevalence's for 8^{th}, 10^{th} and 12^{th} graders were 2.7%, 3.3% and 3.5% respectively. While these statistics demonstrate a decline in SC use amongst youth, hospitalizations due to serious adverse effects and deaths following ingestion of SCs, including AB-CHMINACA, AB-PINACA and THJ-2201, by adolescents and teens continue to occur (see Factor 6).

Based on the sampling from forensic psychiatric centers, Dresen and colleagues (Dresen et al., 2010) found that while being admitted to treatment centers 63.3% of patients continue to abuse SCs. According to the testimony given by the Deputy Director of the Office of National Drug Control Policy (ONDCP) to the U.S. Senate Caucus on International Narcotics Control Board (September 25, 2013), current drug testing misses significant populations of synthetic cannabinoid users. In an example described in his testimony, a study found that in a sample of men 30 years old or younger within the District of Columbia parole and probation system, 39 percent of those who passed a traditional drug screen tested positive for SCs.[7] The study further showed that between one-quarter and one-third of young men who were tested in the Washington, D.C. criminal justice system had positive test results for SCs, regardless of the outcome of the traditional drug screen.[8] In addition to the characterized psychoses, toxicological analysis of drivers with impairment has identified a synthetic cannabinoid in their systems (Yeakel and Logan, 2013).

In October 2013, a 40 year old male was killed following an automobile accident in Tulsa, Oklahoma. Toxicology results of the driver of the other car involved in accident showed presence of AB-FUBINACA and AB-PINACA in biological samples (see Factor 6).

Several SCs have been shown to display higher potency in vitro and in vivo when compared to Δ^9-THC (Compton et al., 1992; Wiley et al., 1998; Wiebelhaus et al., 2012). Smoking mixtures of these substances abused for the purpose of achieving intoxication have resulted in numerous emergency room visits and calls to poison control centers. Abuse of SCs and their products has

[7] Office of National Drug Control Policy. *Community Drug Early Warning System: The CDEWS Pilot Project, 13.* September 13, 2013.
[8] *Id*. p. vi.

been characterized with both acute and long term public health and safety issues. Distinct pharmacological properties and metabolism of SCs have been suggested to contribute to the observed toxicity associated with the abuse of SCs (Fantegrossi et al., 2014).

Most users of SCs abuse these substances by smoking the product following application to plant material. Recently, law enforcement has also been encountering new variations of SCs in liquid form. The liquids contain one or more SC(s), including examples such as AB-CHMINACA and AB-PINACA as well as previously controlled substances including AB-FUBINACA and XLR11. Users have been identified applying the liquid to hookahs (an instrument for vaporizing and smoking a given material whereby the smoke or vapor passes through a water basin prior to inhalation), vaporizers (also known as "vaping" or an "e-cigarette," which allows the user to administer a liquid to be aerosolized and then inhaled), and hookah pens (a type of vaporizer, often much smaller and intended for increased discretion while smoking). As reported by users, specifically adolescents, this method of vaporizing and inhaling SCs is viewed as being safer than traditional smoking (blunt, pipe, cigarette, etc.) (NIDA online, 2014). In the study conducted by Bonar et al. (2014), while 91% of SC users reported inhalation of the product via a cigarette or blunt, 27% of the respondents also reported using methods that included vaporization, water pipe, bong, or hookah as a delivery method.

Factor 5: The Scope, Duration, and Significance of abuse

AB-CHMINACA, AB-PINACA and THJ-2201 are SCs that have pharmacological effects similar to the schedule I hallucinogen Δ^9- THC. Following multiple scheduling actions in an attempt to safeguard the public from the adverse effects and safety issues associated with SCs misuse and abuse, continued encounters in large numbers by law enforcement and health care professionals indicate that abuse of these substances and their products continue to be popular. With the passing of each Federal action, drug manufacturers and suppliers are adapting at an alarmingly quick pace to switch to new, non-controlled variations of SCs.

Poison control centers continue to report toxic exposures to SCs and their associated products. These substances remain a threat to both the short- and long-term public health and safety. Exposures to SCs were first reported to the AAPCC in 2011 (Table 8). The AAPCC report published on April 23, 2015, showed a marked spike in poison center exposure calls

throughout the United States in 2015. The AAPCC reported 1,512 exposure calls in April 2015, representing an almost three-fold increase in exposures to SCs as compared to the previous largest monthly tally (657 exposures in January 2012) since reporting began in 2011. For the first time since reporting began by the AAPCC in 2011, the number of cases in 2015 has dramatically risen, more than doubling those reported in 2014. The numbers of exposure cases for SCs reported in 2015 were the highest ever recorded. In addition, a majority of exposure incidents from 2011 to the present resulted in individuals seeking medical attention at health care facilities.[9] In 2016, numbers of exposure calls have dropped again, mirroring those of 2013.

Table 8. Exposure cases of synthetic cannabinoids as reported to poison centers*

YEAR	# OF CASES
2011	6,968
2012	5,230
2013	2,668
2014	3,682
2015	7,779
2016 (through December 31, 2016)	2,695

* AAPCC, January, 2017

The following tables (Table 9; Table 10) represent exhibits/reports obtained through both STRIDE and NFLIS that correspond to the specific drug listed.

[9] The content of this report does not necessarily reflect the opinions or conclusions of the American Association of Poison Control Centers (AAPCC). AAPCC (http://www.aapcc.org) maintains the national database of information logged by the country's 55 Poison Control Centers (PCCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g. an ingestion, inhalation, topical exposure, etc.) or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

Table 9. Reports obtained through the NFLIS database[§]

NFLIS[* §]				
DRUG	**2013**	**2014**	**2015**	**2016**
AB-CHMINACA	0	2,618	6,945	919
AB-PINACA	981	5,243	2,539	260
THJ-2201	0	539	199	69

* Query date: November 10, 2016.

§ Laboratories reporting to NFLIS include State, local and other federal laboratories (not including DEA).

Table 10. STRIDE and STARLiMS Records - January 2013 through November 2016* (Query date: November 10, 2016):**

	NUMBER OF RECORDS
AB-CHMINACA	635
AB-PINACA	976
THJ-2201	190

* No reports identified in STRIDE regarding AB-PINACA prior to January 2013. No reports of AB-CHMINACA or THJ-2201 prior to January 2014.

** Data were queried through November 10, 2016.

THJ-2201 was first reported in September 2013 while AB-CHMINACA was first reported in February of 2014. AB-PINACA was encountered on the illicit drug market as early as March 2013. From December 2013 through May 2015, CBP reported select encounters of these substances with most shipments originating in China and intended for destinations within the United States: AB-CHMINACA–50 seizures involving 56.29 kg; AB-PINACA–11 seizures involving 15 kg; THJ-2201–6 seizures involving 5.5 kg (Appendix 2, Table 11).[10] The DEA has reported multiple encounters of large quantities of AB-CHMINACA, AB-PINACA and THJ-2201 that have been confirmed by forensic laboratories (STRIDE and/or NFLIS).

Summary

The abuse of SCs is characterized in the scientific literature and by law enforcement encounters with reported adverse health effects. Numerous calls have been received by poison control centers regarding the abuse of SCs that have resulted in visits to emergency departments. Following legislative control of JWH-018, JWH-200, JWH-073, CP-47,497, and

[10] Correspondence from CBP to DEA, (December 2013–May 2015).

cannabicyclohexanol, by FDASIA in July 2012 and temporary control of UR-144, XLR11, and AKB48 in May 2013 and PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA in February 2014, law enforcement has once again begun encountering novel SCs including AB-CHMINACA, AB-PINACA and THJ-2201.

Factor 6: What, if Any, Risk There is to the Public Health

Clinical symptoms as reported from overdoses with AB-CHMINACA and AB-PINACA in particular have included excited delirium, seizure, coma, agitation, myocardial infarction, convulsions, difficulty breathing, and an altered state of consciousness (correspondence from law enforcement/laboratory/clinical personnel). As mentioned in Factor 4, the HHS reported that despite the increasing public recognition of the harms of SCs, multiple groups, including athletes, military personnel, employees who undergo frequent drug testing, and individuals seeking intoxication, continue to abuse SCs while hoping to evade detection.

Since abusers obtain these drugs through unknown sources, purity of these drugs is uncertain, thus posing significant adverse health risk to these users (EMCDDA, 2009, Dresen et al., 2010). From October 2013 through the present, multiple deaths and severe overdoses have occurred involving AB-CHMINACA, AB-PINACA and/or THJ-2201 (Trecki et al., 2015). Details of these events are summarized below.

- In October 2013, a 40-year-old male was killed in Tulsa, Oklahoma, following a head on motor vehicle collision. Toxicology results of the opposing driver detected AB-PINACA and AB-FUBINACA in biological samples.[11]
- In early 2014, two deaths were reported (19-year-old, Angola, Indiana; 37-year-old male, Omaha, Nebraska) involving AB-PINACA. Cause of death in both cases was deemed synthetic cannabinoid-related.[12]
- In April 2014, a 21-year-old female in Lafayette, Louisiana, died with the cause of death determined to be drowning with contribution of poly-drug toxicity. Laboratory results detected AB-CHMINACA in both drug evidence and biological samples.[13]

[11] Correspondence from US Postal Inspection Service to DEA, 3/28/2014.
[12] Correspondence from AIT Laboratories to DEA, 06/03/2014.
[13] Correspondence from Lafayette, Parish Coroner's Office to DEA, 05/29/2014.

- In April 2014, a male presented at a local emergency department in Mobile, Alabama with excited delirium following ingestion of a synthetic cannabinoid. Laboratory results on drug evidence detected AB-CHMINACA.[14]
- In April 2014, a 38-year-old male in Bay Minette, Alabama, died following ingestion of a synthetic cannabinoid product. Laboratory results detected AB-CHMINACA in biological samples.[15]
- In May 2014, an 18-year-old male in Seattle, Washington, suffered adverse effects following ingestion of a synthetic cannabinoid product "Black Voodoo." Laboratory results on drug evidence and biological samples detected AB-CHMINACA.[16]
- In May 2014, a 32-year-old male in Corvallis, Oregon, died following ingestion of a synthetic cannabinoid product "Scooby Snax." Laboratory results on drug evidence and biological samples detected AB-CHMINACA. The cause of death as determined by the medical examiner was "toxic effects of synthetic cannabinoids: AB-CHMINACA".[17]
- In May/June 2014, over 29 individuals in Gainesville, Florida, presented at local emergency departments with seizures and comas following ingestion of a synthetic cannabinoid. Laboratory analysis conducted on biological samples from 13 of the patients identified AB-CHMINACA as the drug responsible for the effects listed previously.[18]
- In June 2014, a 14-year-old year old male in New Orleans, Louisiana, experienced convulsions and severe shaking after ingesting a synthetic cannabinoid product "Mojo." Laboratory results on drug evidence and biological samples detected AB-CHMINACA.[19,20]
- In June 2014, a 13-year-old female in Irving, Texas, experienced convulsions after ingesting a synthetic cannabinoid product. Laboratory results on biological samples detected AB-CHMINACA.[21]

[14] STRIDE, DEA.
[15] Correspondence from AIT Laboratories to DEA, 08/07/2014.
[16] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.
[17] Report from the Office of the State Medical Examiner (OR) to DEA, 08/07/2014.
[18] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.
[19] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.
[20] Correspondence from Jefferson Parish Sheriff's Office to DEA, 07/10/2014.
[21] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.

- In June 2014, a 16-year-old male and 17 year old female in Atlantic City, New Jersey, experienced delirium after ingesting a liquid synthetic cannabinoid ingested through a hookah pen. Laboratory results on drug evidence detected AB-PINACA.[22]
- In June 2014, a 39-year-old male in Baton Rouge, Louisiana, was transported by emergency medical services (EMS) to a local emergency department after experiencing severe agitation following ingestion of a synthetic cannabinoid product. Laboratory results on biological samples detected AB-CHMINACA.[23]
- In July 2014, a 19-year-old male in Newport Beach, California, died following ingestion of a synthetic cannabinoid product. Laboratory analysis of drug evidence and biological samples detected AB-CHMINACA.[24] The cause of death as determined by the medical examiner was toxic effects of synthetic cannabinoid AB-CHMINACA.[25]
- In July 2014, a 10-month-old infant in Shreveport, Louisiana, was admitted to the prenatal intensive care unit (PICU) following ingestion of a synthetic cannabinoid product. Laboratory analysis of drug evidence and biological samples detected AB-CHMINACA.[26]
- In August 2014, three juvenile females (14-, 15- and 17-years-old) in St. Louis, Missouri, suffered a loss of consciousness and seizures following ingestion of a synthetic cannabinoid product. Laboratory results of evidence detected AB-PINACA and AB-CHMINACA.[27]
- In August 2014, over 44 individuals in Manchester, New Hampshire, presented at local emergency departments suffering seizures and serious medical reactions following the ingestion of synthetic cannabinoid products. Laboratory analysis of evidence collected detected multiple SCs including AB-CHMINACA.[28]
- In August 2014, a 34-year-old male died in Beaumont, TX following ingestion of a synthetic cannabinoid product. Laboratory results detected THJ-2201 in biological samples.[29]

[22] Correspondence from Atlantic City PD to DEA, 07/02/2014.
[23] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.
[24] Correspondence from Orange County Crime Laboratory to DEA, 08/07/2014.
[25] Correspondence from Orange County Sheriff's Office to DEA, 11/21/2014.
[26] Correspondence from Shreveport, Louisiana PD to DEA, 10/07/2014.
[27] Correspondence from Franklin County Missouri Sheriff's Office to DEA, 08/26/2014.
[28] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 08/26/2014.
[29] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 01/28/2015.

- In August 2014, a 45-year-old male died in Austin, TX following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was atherosclerotic and hypertensive-type cardiovascular disease, with other significant factors including methamphetamine and synthetic cannabinoid (THJ-2201 and AB-PINACA) toxicity.[30]
- In September 2014, four juveniles were taken to local emergency departments following ingestion of a synthetic cannabinoid e-liquid identified as "Cloud 9." Laboratory results of the product detected AB-PINACA.[31]
- In September 2014, a 58-year-old male died following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was AB-CHMINACA and ethanol toxicity.[32]
- In October 2014, a 48 year old male died following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was complications of hypertensive cardiovascular disease, with another significant factor of synthetic cannabinoid (AB-CHMINACA) toxicity.[33]
- In November 2014, a 13-year-old male died following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was an overdose of AB-CHMINACA, a synthetic cannabinoid, due to recreational drug use.[34]
- In December 2014, a 43-year-old male died following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was a result of sharp force injuries to the right arm (falling through a window) with another significant factor of synthetic cannabinoid (AB-CHMINACA and AB-FUBINACA) toxicity.[35]
- In January 2015, a juvenile female in Mountain Lakes, NJ was transported to a local emergency department following ingestion of a synthetic cannabinoid e-liquid via a hookah pen. Laboratory results of the substance in the hookah pen detected AB-CHMINACA.[36]

[30] Correspondence from Travis County Medical Examiner to DEA, 06/18/2015.
[31] Correspondence from Michigan State Police to DEA, 09/16/2014.
[32] Correspondence from Travis County Medical Examiner to DEA, 06/29/2015.
[33] Correspondence from Travis County Medical Examiner to DEA, 06/18/2015.
[34] Correspondence from Greene County Medical Examiner to DEA, 07/07/2015.
[35] Correspondence from Travis County Medical Examiner to DEA, 06/29/2015.
[36] Correspondence from Mountain Lakes Police Department to DEA, 01/07/2015.

- In January 2015, a 51-year-old male died in Boyle, KY following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was toxic effects of synthetic cannabinoid AB-CHMINACA.[37]
- In January 2015, a 25-year-old male died in Killeen, TX following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was synthetic cannabinoid intoxication (AB-CHMINACA, ABK48 and XLR11).[38]
- In July 2015, a 51-year-old male died in Onondaga County, NY following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was synthetic cannabinoid (AB-CHMINACA and ADB-CHMINACA) intoxication.[39]
- In August 2015, a 36-year-old female died in Onondaga County, NY following ingestion of a synthetic cannabinoid product. The cause of death as determined by the medical examiner was acute synthetic cannabinoid (AB-CHMINACA) intoxication.[40]

Throughout 2013 and 2014, descriptions of overdoses, hospitalizations, severe outbreaks (CDC, 2013a,b,c) and deaths (Behonek et al., 2014; Trecki et al., 2015) involving different SCs have been reported in both scientific publications and in the news media. Human studies intended to investigate the health implications resulting from exposure to these substances are not ethical due to the severe adverse effects associated with ingestion of illicit SCs. However, adverse effects requiring medical attention following ingestion of SCs have been reported by physicians and emergency medical personnel (Griffiths et al., 2010; Vardakou et al., 2010). Common clinical effects observed in emergency rooms as reported by numerous state public health departments, poison control centers, and private organizations include: vomiting, anxiety, agitation, irritability, seizures, hallucinations, tachycardia, elevated blood pressure, loss of consciousness, and non-responsiveness (Forrester et al., 2011; Cohen et al., 2012; Harris and Brown, 2013; Hermanns-Clausen et al., 2013; Zawilska and Wojcieszak, 2013) (see reports from state health departments and poison centers including AAPCC, Appendix 1).

[37] Correspondence from the Office of the Associate Chief Medical Examiner (KY) to DEA, 02/27/2015.
[38] Correspondence from the Department of Defense to DEA, 04/29/2015.
[39] Correspondence from the Medical Examiner's Office, Onondaga County, NY to DEA, 12/22/2015.
[40] Correspondence from the Medical Examiner's Office, Onondaga County, NY to DEA, 12/22/2015.

A 12-month study conducted in 2012 demonstrated that out of 950 self-reported users of various SC's, 2.4% reported having a medical emergency consisting of a combination of panic, anxiety, paranoia, and breathing difficulties requiring treatment (Winstock and Barratt, 2013). Data from this study also demonstrated that users who reported seeking emergency treatment were significantly younger than those who did not report seeking treatment (Winstock and Barratt, 2013). These data correspond to those reported by SAMSHA demonstrating that youth, specifically those aged 12 to 17 years old, comprise a large percentage of users requiring emergency medical attention (figure 4) (SAMSHA, 2014.

Since abusers obtain SCs including AB-CHMINACA, AB-PINACA, and THJ-2001 through unknown sources, the identity, purity, and quantity of these substances is uncertain and inconsistent, thus posing significant adverse health risks to users. There are no accepted medical uses for AB-CHMINACA, AB-PINACA, and THJ-2201 within the United States. Regardless, SCs continue to be easily available and abused by diverse populations. Factors such as lack of detailed product analysis and dosage variations between various packages and batches present a significant danger to an abusing individual (Auwarter et al., 2009; Hudson et al., 2010). Similar products have been found to vary in the amount and type of synthetic cannabinoid laced on the plant material, which could be one explanation for the numerous emergency department admissions that have been connected to these substances (Vardakou et al., 2010; Vearrier and Osterhoudt, 2010; Schneir et al., 2011; Fattore and Fratta, 2011).

By sharing pharmacological similarities with schedule I substances such as Δ^9-THC, JWH-018 and other temporarily and permanently controlled schedule I SCs (Weissman et al., 1982; Compton et al., 1992; Wiley et al., 1998), these SCs pose a risk to the abuser. The chronic abuse of products laced with SCs has been linked to addiction and withdrawal (Vardakou et al., 2010).

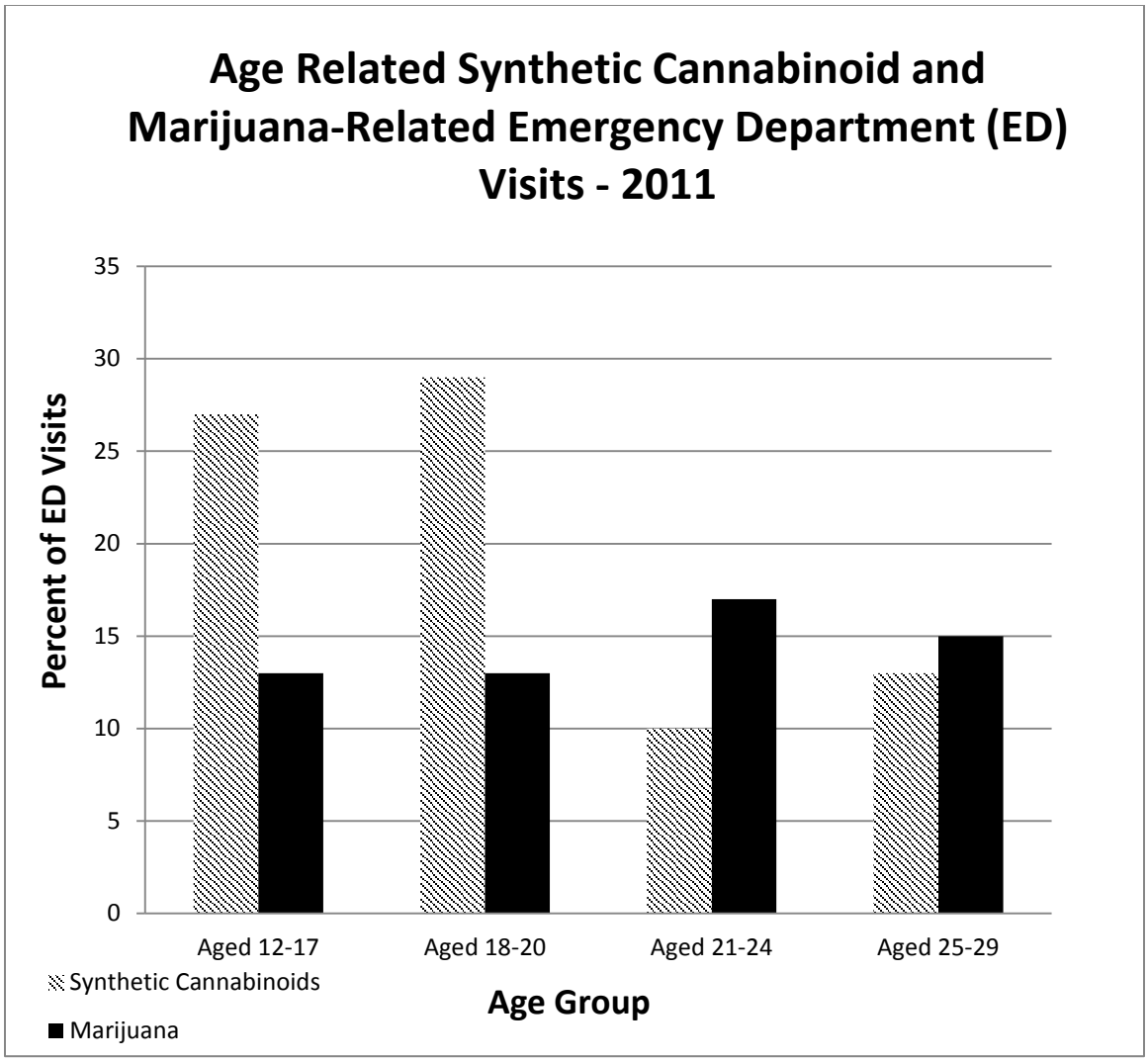

Figure 4. Age-related emergency department visits involving synthetic cannabinoids and marijuana (SAMHSA, 2014).

In June 2016 in Phoenix, AZ, local law enforcement discovered a synthetic drug laboratory. Evidence collected at the scene included products that contained a SC alone (one exhibit contained a 5F-AMB, a second exhibit contained AB-PINACA), while a third exhibit contained mixtures of both a SC (AB-PINACA) and a synthetic opioid, positively identified as acetyl fentanyl.[41]

Factor 7: Its Psychic or Physiological Dependence Liability

[41] Correspondence from Arizona Department of Public Safety to DEA, June 14, 2016.

As stated by the HHS, AB-CHMINACA, AB-PINACA and THJ-2201 have pharmacological profiles that are similar to other schedule I SCs. Although there are no clinical studies evaluating dependence liabilities specific for AB-CHMINACA, AB-PINACA and THJ-2201, the pharmacological profiles of these substances strongly suggest that they possess dependence liabilities that are qualitatively similar to, and potentially stronger than Δ^9-THC (schedule I) or marijuana (schedule I) and likely to be similar to other synthetic cannabinoids such as, JWH-018. The euphoric and mood altering effects of SCs as described by users are similar to those of cannabis.

The HHS described an audit of patients presenting for help in discontinuing their SC abuse from Auckland, New Zealand (Macfarlane and Christie, 2015). Common withdrawal symptoms of SCs were agitation, irritability, anxiety and mood swings, requiring management with benzodiazepines and/or an atypical antipsychotic such as quetiapine. Patients with the SC withdrawal were the third largest group admitted to inpatient detoxification. Many patients required medical management and intensive support.

Every-Palmer (2010) has reported of the recurrence of psychosis in stable individuals with a previous history of psychosis. Every-Palmer (2011) followed up the initial communication with interviews of 15 patients with severe mental illness in a New Zealand forensic and rehabilitation service. In a case report, dependence syndrome corresponding to the ICD-10 and DSM-IV criteria and the physical withdrawal resembled cannabis dependence (Zimmermann et al., 2009) after the consumption of "Spice Gold." Spice Gold has been found to contain a mixture of the synthetic cannabinoid substances JWH-018 and CP-47-497

Factor 8: Whether the Substance is an Immediate Precursor of a Substance Already Controlled

AB-CHMINACA, AB-PINACA and THJ-2201 are not immediate precursors of any controlled substance of the CSA.

III. Findings for Schedule Placement Pursuant to 21 U.S.C. 812(b)

21 U.S.C. 812(b) requires the evaluation of a substance's abuse potential, accepted medical use, and safety for use under medical supervision for scheduling under the CSA as a controlled substance. After consideration of the above eight factors determinative of control of a substance (21 U.S.C. 811(c)), and a review of the scientific and medical evaluation and scheduling recommendation provided by the HHS, the DEA finds that AB-CHMINACA, AB-PINACA and THJ-2201 meet the following criteria for placement in schedule I of the CSA pursuant to 21 U.S.C. 812 (b)(1).

1) *AB-CHMINACA, AB-PINACA and THJ-2201have a high potential for abuse that is comparable to other schedule I substances such as Δ^9-THC, JWH-018, AM2201, ADB-PINACA and AB-FUBINACA.*

AB-CHMINACA, AB-PINACA and THJ-2201 are synthetic substances that produce cannabinoid agonist-like pharmacological effects that are similar to those produced by schedule I substances such as Δ^9-THC, JWH-018, AM2201, ADB-PINACA, AB-FUBINACA and other synthetic cannabinoids. AB-CHMINACA, AB-PINACA and THJ-2201, similar to other Schedule I SCs, bind to and activate CB1 receptor in vitro and substitutes for THC in drug discrimination tests. The pharmacological similarity of AB-CHMINACA, AB-PINACA and THJ-2201 to Δ^9-THC makes it reasonable to assume that their potential for abuse is high and would be similar to that of JWH-018, AM2201, ADB-PINACA and AB-FUBINACA which are controlled in schedule I of the CSA. NFLIS details over 20,306 reports from forensic laboratories identifying AB-CHMINACA, AB-PINACA and THJ-2201 for a period from January 2013 through November 2016. In addition, STRIDE and STARLiMS have 1,801 reports involving AB-CHMINACA, AB-PINACA and THJ-2201 from January 2013 through November 2016.

2) *AB-CHMINACA, AB-PINACA and THJ-2201 have no currently accepted medical use in treatment in the United States.*

According to the HHS, there are no approved NDAs for AB-CHMINACA, AB-PINACA and THJ-2201 in the United States. There are no known medical uses for AB-CHMINACA, AB-

PINACA and THJ-2201. Therefore, AB-CHMINACA, AB-PINACA and THJ-2201 have no currently accepted medical use in the United States.

3) *There is a lack of accepted safety for use of AB-CHMINACA, AB-PINACA and THJ-2201under medical supervision.*

Because AB-CHMINACA, AB-PINACA and THJ-2201 have no approved medical use and have not been thoroughly investigated as new drugs, their safety for use under medical supervision is not determined. Thus, there is a lack of accepted safety for use of these substances under medical supervision.

References

AAPCC (American Association of Poison Control Centers) 2016. Synthetic Cannabinoids. www.aapcc.org/alerts/synthetic-marijuana/

Atwood BK, Huffman J, Straiker A, Mackie K (2010). JWH018, a common constituent of 'Spice' herbal blends, is a potent and efficacious cannabinoid CB receptor agonist. British Journal of Pharmacology 160:585–593.

Aung MM, Griffin G, Huffman JW, Wu M-J, Keel C, Yang B, Showalter VM, Abood ME, and Martin BR (2000). Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB1 and CB2 receptor binding. Drug and Alcohol Dependence 60:133–140.

Aüwarter V, Dresen S, Weinmann W, Muller M, Putz M, Ferreiros N (2009). 'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? Journal of Mass Spectrometry 44:832–837.

Balster RL, Bigelow GE (2003). Guidelines and methodological reviews concerning drug abuse liability assessment. Drug and Alcohol Dependence 70(3 Suppl):S13-40

Banister SD, Moir M, Stuart J, Kevin RC, Wood KE, Longworth M, Wilkinson SM, Beinat C, Buchanan AS, Glass M, Connor M, McGregor IS, Kassiou M (2015). Pharmacology of Indole and Indazole Synthetic Cannabinoid Designer Drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. ACS Chemical Neuroscience 6(9):1546-59.

Behonick G, Shanks KG, Firchau DJ, Mathur G, Lynch CF, Nashelsky M, Jaskuierny DJ, Meroueh C (2014). Four postmortem case reports with quantitative detection of the synthetic cannabinoid 5F-PB-22. Journal of Analytical Toxicology 38(8):559–62.

Bonar EE, Ashrafioun L, Ilgen MA (2014). Synthetic cannabinoid use among patients in residential substance use disorder treatment: Prevalence, motives, and correlates. Drug and Alcohol Dependence 143:268–271.

CDC (Centers for Disease Control and Prevention) (2013a). Acute kidney injury associated with synthetic cannabinoid use–multiple states, 2012. Morbidity Mortality Weekly Report 62(6):93–8.

CDC (Centers for Disease Control and Prevention) (2013b). Notes from the Field: Severe Illness Associated with Synthetic Cannabinoid Use — Brunswick, Georgia, 2013. MMWR Morbidity Mortality Weekly Report 62(46):939.

CDC (Centers for Disease Control and Prevention) (2013c). Notes from the Field: Severe Illness Associated with Reported Use of Synthetic Marijuana — Colorado, August–September 2013. MMWR Morbidity Mortality Weekly Report 62(49):1016–17 .

Cohen J, Morrison S, Greenberg J, Saidinejad M (2012). Clinical presentation of intoxication due to synthetic cannabinoids. Pediatrics 129(4):e1064–1067.

Compton DR, Gold LH, Ward SJ, Balster RL, Martin BR (1992). Aminoalkylindole analogs: cannabimimetic activity of a class of compounds structurally distinct from delta 9-tetrahydrocannabinol. The Journal of Pharmacology and Experimental Therapeutics 263:1118–1126.

Compton DR, Rice KC, De Costa BR, Razdan RK, Melvin LS, Johnson MR, Martin BR (1993). Cannabinoid structure-activity relationships: correlation of receptor binding and in vivo activities. The Journal of Pharmacology and Experimental Therapeutics 265:218–226.

Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA (2014). Synthetic cannabinoids: Epidemiology, pharmacodynamics, and clinical implications. Drug and Alcohol Dependence 144:12–41.

DEA (2009). "Spice" – Plant material(s) laced with synthetic cannabinoids or cannabinoid mimicking compounds. In: Microgram Bulletin, vol. 42, pp 23–24.

DEA (2012). Schedules of Controlled Substances: Placement of 1-Butyl-3-(1-naphthoyl)indole (JWH-073), 1-pentyl-3-(1-naphtoyl)indole (JWH-018), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol (cannabicyclohexanol and CP-47,497 C8 homologue) into Schedule I: Background, Data, and Analysis: Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b).

DEA (2013). 1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole (UR-144), 1-(5-fluoro-pentyl)-3-(2,2,3,3-tetramethylcyclopropoyl)indole (5-fluoro-UR-144; XLR11) and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA, AKB48): Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for Temporary Scheduling. 78 FR 28735.

DEA (2014) Quinolin-8-yl 1-pentyl-1H-indole-3-carboxylate (PB-22; QUPIC), quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22), N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB-FUBINACA) and N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (ADB-PINACA): Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for Temporary Scheduling. 79 FR 7577.

Diao X, Scheidweiler KB, Wohlfarth A, Zhu M, Pang S, Huestis MA (2016). Strategies to distinguish new synthetic cannabinoid FUBIMINA (BIM-2201) intake from its isomer THJ-2201: metabolism of FUBIMINA in human hepatocytes. Forensic Toxicolology 34:256–267.

Dresen S, Ferreiros N, Putz M, Westphal F, Zimmermann R, Auwarter V (2010). Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. Journal of Mass Spectrometry 45:1186–1194.

Durand D, Delgado LL, de la Parra-Pellot DM, Nichols-Vinueza D (2013). Psychosis and severe rhabdomyolysis associated with synthetic cannabinoid use. Clinical Schizophrenia & Related Psychoses 21:1–13.

EMCDDA (2009) Understanding the 'Spice' Phenomenon. In: The European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal.

Erratico C, Negreira N, Norouzizadeh H, Covaci A, Neels H, Maudens K, van Nuijs AL (2015). In vitro and in vivo human metabolism of the synthetic cannabinoid AB-CHMINACA. Drug Testing and Analysis 7(10):866-76.

Every-Palmer S (2010). Warning: legal synthetic cannabinoid-receptor agonists such as JWH-018 may precipitate psychosis in vulnerable individuals. Addiction 105(10):1859–60.

Every-Palmer S (2011). Synthetic cannabinoid JWH-018 and psychosis: an explorative study. Drug and Alcohol Dependence 117(2-3):15–7.

Fantegrossi WE, Moran JH, Radominska-Pandya A, Prather PL (2014). Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to delta9-THC: Mechanism underlying greater toxicity. Life Sciences 97(1):45–54.

Fattore L, Fratta W (2011). Beyond THC: the new generation of cannabinoid designer drugs. Frontiers in Behavioral Neuroscience 5:1–12.

Forrester MB, Kleinschmidt K, Schwarz E, Young A (2011). Synthetic cannabinoid exposures reported to Texas poison centers. Journal of Addiction Disorders 30(4):351–8.

Griffiths P, Sedefov R, Gallegos A, Lopez D (2010). How globalization and market innovation challenge how we think about and respond to drug use: 'Spice' a case study. Addiction 105:951–953.

Harris CR, Brown A (2013). Synthetic cannabinoid intoxication: a case series and review. Journal of Emergency Medicine 44(2):360–6.

Hermanns-Clausen M, Kneisel S, Szabo B, Auwärter V (2013). Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. Addiction 108(3):534–44.

Hudson S, Ramsey J, King L, Timbers S, Maynard S, Dargan PI, Wood DM (2010). Use of high-resolution accurate mass spectrometry to detect reported and previously unreported cannabinomimetics in "herbal high" products. Journal of Analytical Toxicology 34:252–260.

Huffman JW, Dong D, Martin BR, Compton DR (1994). Design, synthesis and pharmacology of cannabimimetic indoles. Bioorganic and Medicinal Chemistry Letters 4:563–566.

Huffman JW, Yu S, Showalter V, Abood ME, Wiley JL, Compton DR, Martin BR, Bramblett RD, Reggio PH (1996). Synthesis and pharmacology of a very potent cannabinoid lacking a phenolic hydroxyl with high affinity for the CB2 receptor. Journal of Medicinal Chemistry 39(20):3875–7.

Huffman JW, Liddle J, Yu S, Aung MM, Abood ME, Wiley JL, Martin BR (1999). 3-(1',1'-Dimethylbutyl)-1-deoxy-delta8-THC and related compounds: synthesis of selective ligands for the CB2 receptor. Bioorganic and Medicinal Chemistry 7(12):2905–14.

Huffman JW (2009). Cannabimimetic indoles, pyrroles, and indenes: Structure-activity relationships and receptor interactions. Cannabinoid Receptors, Reggio PH, Ed, Chapter 3, 49–98, Humana, New York.

Jaenicke NJ, Pogoda W, Paulke A, Wunder C, Toennes SW (2014). Retrospective analysis of synthetic cannabinoids in serum samples – epidemiology and consumption patterns. Forensic Science International 242:81–87Johnston, LD, O'Malley, PM, Miech, RA, Bachman, JG, Schulenberg, JE (2015). Monitoring the Future national survey results on drug use: 1975–2014: Overview, key findings on adolescent drug use. Ann Arbor: Institute for Social Research, The University of Michigan, 90pp.

Lewin AH, Seltzman HH, Carroll FI, Mascarella SW, Reddy A (2014). Minireview. Emergence and properties of spice and bath salts: A medicinal chemistry perspective. Life Science 97(1):9–19.

Lindigkeit R, Boehme A, Eiserloh I, Luebbecke M, Wiggermann M, Ernst L, Beuerle T (2009). Spice: a never ending story? Forensic Science International 191:58–63.

Macfarlane V, Christie G (2015). Synthetic cannabinoid withdrawal: A new demand on detoxification services. Drug Alcohol Review Epub Jan 15.

Manera C, Tuccinardi T, Martinelli A (2008). Indoles and related compounds as cannabinoid ligands. Mini-Reviews in Medicinal Chemistry 8:370–387.

McKeever RG, Vearrier D, Jacobs D, LaSala G, Okaneku J, Greenberg MI (2015). K2-Not the spice of life; Synthetic cannabinoids and ST elevation myocardial infarction: A case report. Journal of Medical Toxicology 11(1): 129-131.

Melvin LS, Johnson MR, Harbert CA, Milne GM, and Weissman A (1984). A cannabinoid derived prototypical analgesic. Journal of Medicinal Chemistry 27(1):67–71.

NIDA (2014a). National Institute on Drug Abuse. In vitro pharmacology: Functional study of THJ-2201 at the CB1 receptor. Annie Otto-Bruc, Study number: 100015149, December 18, 2014.

NIDA (2015). National Institute on Drug Abuse. In vitro pharmacology: Binding study of THJ-2201 at the CB1 receptor. Annie Otto-Bruc, Study number: 100019333, January, 2015

NIDA (2014b). National Institute on Drug Abuse. THJ-2201: Test of substitution for the discriminative stimulus effects of Delta(9)-THC. Gatch MB and Forster MJ. Contract: N01DA-13-8908. December 1, 2014.

NIDA online (2014). http://www.drugabuse.gov/publications/drugfacts/electronic-cigarettes-e-cigarettes

NFLIS (2016). National Forensic Laboratory Information System. Drug Enforcement Administration.

Ogata J, Uchiyama N, Kikura-Hanajiri R, Goda Y (2013). DNA sequence analyses of blended herbal products including synthetic cannabinoids as designer drugs. Forensic Science International 227:33–41.

Oluwabusi OO, Lobach L, Akhtar U, Youngman B, Ambrosini PJ (2012). Synthetic cannabinoid-induced psychosis: two adolescent cases. Journal of Child and Adolescent Psychopharmacology 22(5):393–395.

ONDCP (Office of National Drug Control Policy), 2014. Synthetic Marijuana.

SAMHSA (2012). The DAWN report: Drug-related emergency department visits involving synthetic cannabinoids (December 4, 2012), Rockville, MD.

SAMHSA (2014). The CBHSQ Report – Update: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids (October 16, 2014). Rockville, MD.

Seely KA, Lapoint J, Moran JH (2012). Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. Progress in Neuropsychopharmacology & Biological Psychiatry 39(2): 234–243.

Schwartz MD, Trecki J, Edison LA, Steck AR, Arnold JK, Gerona RR (2015). A Common Source Outbreak of Severe Delirium Associated with Exposure to the Novel Synthetic Cannabinoid ADB-PINACA. Journal of Emergency Medicine 48(5):573-80.

Scheidweiler KB, Yarvis MJY, Huesetis MA (2015). Nontargeted SWATH acquisition for identifying 47 synthetic cannabinoid metabolites in human urine by liquid chromatography-high-resolution tandem mass spectrometry. Analytical and Bioanyltical Chemistry 407:883–897.

Schifano F, Corzazza O, Deluca P, Davey Z, Di Furia L, Farre M, Flesland L, Mannonen M, Pagani S, Peltoniemi, T, Pezzolesi C, Scherbaum N, Siemann H, Skutle A, Torrens M, Van der Kreeft P (2009). Psychoactive drug or mystical incense? Overview of online available information on Spice products. International Journal of Culture and Mental Health 2:137–144.

Schneir AB, Cullen J, Ly BT (2011). "Spice" girls: synthetic cannabinoid intoxication. The Journal of Emergency Medicine 40:296–299.

Schuster CR, Johanson CE (1988). Relationship between the discriminative stimulus properties and subjective effects of drugs. Psychopharmacology Series 4:161-75.

Shevyrin V, Melkozerov V, Nevero A, Eltsov O, Morzherin Y, Shafran Y (2014). 3-Naphthoylindazoles and 2-naphthoylbenzoimidazoles as novel chemical groups of synthetic cannabinoids: Chemical structure elucidation, analytical characteristics and identification of the first representatives in smoke mixtures. Forensic Science International 242; 72–80.

STRIDE (2014). System to Retrieve Information from Drug Evidence. Drug Enforcement Administration.

Tai S, Fantegrossi WE (2014). Synthetic Cannabinoids: Pharmacology, Behavioral Effects, and Abuse Potential. Current Addiction Reports 1(2):129-136.

Takayamaa T, Suzukia M, Todorokia K, Inouea K, Mina JZ, Kikura-Hanajirib R, Godab Y Toyo'okaa T (2014). UPLC/ESI-MS/MS-based determination of metabolism of several new illicit drugs, ADB-FUBINACA, AB-FUBINACA, AB-PINACA, QUPIC, 5F-QUPIC and α-PVT, by human liver microsome. Biomedical Chromatography 28: 831–838.

Thomsen R, Nielsen LM, Holm NB, Rasmussen HB, Linneta K, INDICES Consortium (2014). Synthetic cannabimimetic agents metabolized by carboxylesterases. Drug Testing and Analysis (E-pub, Oct. 24, 2014).

Trecki J, Gerona RR, Schwartz MD (2015). Synthetic Cannabinoid–Related Illnesses and Deaths. New England Journal of Medicine 373(2):103–107.

Tyndall JA, Gerona R, De Portu G, Trecki J, Elie MC, Lucas J, Slish J, Rand K, Bazydlo L, Holder M, Ryan MF1, Myers P, Iovine N, Plourde M, Weeks E, Hanley JR, Endres G, St Germaine D, Dobrowolski PJ, Schwartz M (2015). An outbreak of acute delirium from exposure to the synthetic cannabinoid AB-CHMINACA. Clinical Toxicology (Phila) 53(10):950-6.

Uchiyama N, Kikura-Hanajiri R, Ogata J, Goda Y (2010). Two new-type cannabimimetic quinolinyl carboxylates, QUPIC and QUCHIC, two new cannabimimetic carboxamide derivatives, ADB-FUBINACA and ADBICA, and five synthetic cannabinoids detected

with a thiophene derivative a-PVT and an opioid receptor agonist AH-7921 identified in illegal products. Chemical analysis of synthetic cannabinoids as designer drugs in herbal products. Forensic Science International 198:31–38.

Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y (2012a). Identification of two new-type synthetic cannabinoids, N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APICA) and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA), and detection of five synthetic cannabinoids, AM-1220, AM-2233, AM-1241, CB-13 (CRA-13), and AM-1248, as designer drugs in illegal products. Forensic Toxicology 30:114–125.

Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y (2012b). URB-754: A new class of designer drug and 12 synthetic cannabinoids detected in illegal products. Forensic Science International 227(1-3):21–32.

Vandrey R, Dunn KE, Fry JA, Girling ER (2012). A survey to characterize use of spice products (synthetic cannabinoids). Drug and Alcohol Dependence 120:238–241.

Vardakou I, Pistos C, Spiliopoulou C (2010). Spice drugs as a new trend: mode of action, identification and legislation. Toxicology Letters 197:157–162.

Vearrier D, Osterhoudt KC (2010). A teenager with agitation: higher than she should have climbed. Pediatric Emergency Care 26:462–465.

Weissman A, Milne GM, Melvin LS, Jr (1982). Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol. The Journal of Pharmacology and Experimental Therapeutics 223:516–523.

Wiebelhaus JM, Poklis JL, Poklis A, Vann RE, Litchman AH, Wise LE (2012). Inhalation exposure to smoke from synthetic “marijuana” produces cannabimimetic effects in mice. Drug and Alcohol Dependence 126:316–323.

Wells DL, Ott CA (2011). The “new” marijuana. The Annals of Pharmacotherapy 45:414–417.

Wiley JL, Compton DR, Dai D, Lainton JA, Phillips M, Huffman JW, Martin BR (1998). Structure-activity relationships of indole- and pyrrole-derived cannabinoids. The Journal of Pharmacology and Experimental Therapeutics 285:995–1004.

Wiley JL, Marusich JA, Lefever TW, Antonazzo KR, Wallgren MT, Cortes RA, Patel PR, Grabenauer M, Moore KN, Thomas BF (2015). AB-CHMINACA, AB-PINACA, and FUBIMINA: Affinity and Potency of Novel Synthetic Cannabinoids in Producing Δ9-Tetrahydrocannabinol-Like Effects in Mice. Journal of Pharmacology and Experimental Therapuetics, epub Jun 23.

Winstock AR, Barratt MJ (2013). The 12-month prevalence and natrue of adverse experiences resulting in emergency medical prsentations associated with the use of synthetic

cannabinoid products. Human Psychopharmacology: Clinical and Experminetal 28:390–393.

Wurita A, Hasegawa K, Minakata K, Gonmori K, Nozawa H, Yamagishi I, Suzuki O, Watanabe K (2016). Identification and quantification of metabolites of AB-CHMINACA in a urine specimen of an abuser. Legal Medicine (Tokyo) 19:113-8.

Yeakel JK, Logan BK (2013). Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. Journal of Analytical Toxicology 37(8):547–551.

Zawilska JB, Wojcieszak J (2013). Spice/K2 drugs – more than innocent subsitutes for marijuana. International Journal of Neuropsychopharmacology 17(3):509–25.

Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R, Schulz K (2009). Withdrawal phenomena and dependence syndrome after the consumption of “spice gold”. Deutsches Arzteblatt International 106:464–467.

Appendix 1

Public Health

1. Monitoring the Future study results for 2016 (released 12/13/2016) state the use of synthetic marijuana decreased in the past year from 3.1% to 2.7% among 8th graders, from 4.3% to 3.3% among 10th graders, and from 5.2% to 3.5% among 12th graders.
2. Health effects from the drug can be life-threatening and can include (AAPCC, 2016):
    a. Severe agitation and anxiety.
    b. Fast, racing heartbeat and higher blood pressure.
    c. Nausea and vomiting.
    d. Muscle spasms, seizures, and tremors.
    e. Intense hallucinations and psychotic episodes.
    f. Suicidal and other harmful thoughts and/or actions.
    g. http://www.aapcc.org/alerts/synthetic-marijuana/
3. Synthetic cannabinoids, commonly known as "synthetic marijuana," "K2," or "Spice," are often sold in legal retail outlets as "herbal incense" or "potpourri." They are labeled "not for human consumption" to mask their intended purpose and avoid Food and Drug Administration (FDA) regulatory oversight of the manufacturing process. (Office of National Drug Control Policy, 2016).
4. At least 43 States have taken action to control one or more synthetic cannabinoids. (Office of National Drug Control Policy, 2016).
5. Spice users report experiences similar to those produced by marijuana—elevated mood, relaxation, and altered perception—and in some cases the effects are even stronger than those of marijuana. Some users report psychotic effects like extreme anxiety, paranoia, and hallucinations. (National Institute on Drug Abuse, 2015).
6. Spice abusers who were taken to emergency rooms reported symptoms that include: rapid heart rate, vomiting, agitation, violent behavior and suicidal thoughts. Spice abuse can also raise blood pressure and cause reduced blood supply to the heart (myocardial ischemia), and in a few cases it has been associated with a rising number of deaths. Regular users may experience withdrawal and addiction symptoms. (National Institute on Drug Abuse, 2015).
7. CESAR FAX, a publication from the Center for Substance Abuse Research at the University of Maryland (College Park), reported the results from Bonar et al. (2014) describing the results of the study of patients in a Midwestern residential treatment program. Results demonstrated that 71% of those reporting synthetic cannabinoid abuse used a SC-laced product to avoid a positive drug test. The two most common reasons for SC use were "curiosity" (91%) and "to feel good or get high" (89%) (September, 2014).

Appendix 2

Table 11. Selected Reports from Customs and Border Protection Laboratory (December 2013 – May 2015)

Date of Detention	Identified Substance(s)	Detained at	Originated from	Destination	TOTAL WEIGHT
12/27/2013	THJ-2201	San Francisco Intl Mail	China	West Valley City, UT	500 gm
01/03/2014	THJ-2201	San Francisco Intl Mail	China	El Paso, TX	1 kg
02/28/2014	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	1 kg
03/10/2014	AB-CHMINACA	San Francisco Intl Mail	China	Texarkana, AR	1 kg
03/22/2014	THJ-2201	FedEx Anchorage, AK	China	Las Vegas, NV	1 kg
04/29/2014	AB-PINACA	FedEx Anchorage, AK	China	Dothan, AL	1kg
05/09/2014	THJ-2201	San Francisco Intl Mail	China	Las Vegas, NV	500 gm
05/21/2014	THJ-2201	San Francisco Intl Mail	China	Las Vegas, NV	500 gm
05/21/2014	AB-PINACA	San Francisco Intl Mail	China	Spokane, WA	1 kg
05/28/2014	THJ-2201	San Francisco Intl Mail	China	Brooklyn, NY	2 kg
06/26/2014	AB-PINACA	San Francisco Intl Mail	China	Canoga Park, CA	3 kg
07/03/2014	AB-CHMINACA	San Francisco Intl Mail	China	Metairie, LA	100 gm
07/15/2014	AB-CHMINACA	San Francisco Intl Mail	China	Baton Rouge, LA	25 gm
07/16/2014	AB-PINACA	San Francisco	China	Baytown, TX	1 kg

		Intl Mail			
07/28/2014	AB-CHMINACA	Oakland FedEx	China	Amery, WI	500 grams
07/31/2014	AB-CHMINACA	San Francisco Intl Mail	China	Baton Rouge, LA	1 kg
07/31/2014	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	2 kg
07/31/2014	AB-CHMINACA	San Francisco Intl Mail	China	Machesney Park, IL	100 grams
07/31/2014	AB-CHMINACA	San Francisco Intl Mail	China	Machesney Park, IL	100 grams
08/6/2014	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	1 kg
08/6/2014	AB-CHMINACA	San Francisco Intl Mail	China	Hatillo, PR	1.3 kg
08/13/2014	AB-CHMINACA	San Francisco Intl Mail	China	Las Cruces, NM	1.2 kg
08/13/2014	AB-CHMINACA	San Francisco Intl Mail	China	Las Vegas, NV	1 kg
08/19/2014	AB-CHMINACA	San Francisco Intl Mail	China	Las Vegas, NV	2 kg
08/28/2014	AB-PINACA	San Francisco Intl Mail	China	Chatsworth, CA	2 kg
09/2/2014	AB-CHMINACA	San Francisco Intl Mail	China	Baytown, TX	1 kg
09/9/2014	AB-CHMINACA	San Francisco Intl Mail	China	Cypress, TX	1 kg
09/16/2014	AB-CHMINACA	San Francisco Intl Mail	China	Fort Worth, TX	1 kg
09/30/2014	AB-CHMINACA	San Francisco Intl Mail	China	Baytown, TX	1 kg

10/7/2014	AB-CHMINACA	San Francisco Intl Mail	China	Montvale, NJ	3 kg
10/15/2014	AB-CHMINACA	San Francisco Intl Mail	China	Cullom, IL	20 grams
10/17/2014	AB-PINACA	San Francisco Intl Mail	China	Corpus Christi, TX	1 kg
10/30/2014	AB-CHMINACA	San Francisco Intl Mail	China	Pueblo, CO	300 grams
11/4/2014	AB-CHMINACA	San Francisco Intl Mail	China	Richmond, TX	1 kg
11/12/2014	AB-CHMINACA	San Francisco Intl Mail	China	Denver, CO	400 grams
11/19/2014	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	3 kg
11/19/2014	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	4 kg
11/19/2014	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	2 kg
11/19/2014	AB-CHMINACA	San Francisco Intl Mail	China	Pasadena, TX	1 kg
11/25/2014	AB-CHMINACA	San Francisco Intl Mail	China	Baytown, TX	1.5 kg
11/25/2014	AB-CHMINACA	San Francisco Intl Mail	China	Baytown, TX	1.5 kg
11/25/2014	AB-PINACA	San Francisco Intl Mail	China	Canoga Park, CA	2 kg
12/2/2014	AB-CHMINACA	San Francisco Intl Mail	China	Porter Ranch, CA	5 kg
12/3/2014	AB-PINACA	San Francisco Intl Mail	China	Granada Hills, CA	2 kg

12/8/2014	AB-CHMINACA	FedEx Anchorage, AK	China	Miami Lakes, FL	20 grams
12/9/2014	AB-CHMINACA	San Francisco Intl Mail	China	Denver, CO	1 kg
12/9/2014	AB-CHMINACA	San Francisco Intl Mail	China	Blaine, WA	1 kg
12/9/2014	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	500 grams
12/19/2014	AB-PINACA	San Francisco Intl Mail	China	Los Angeles, CA	1 kg
12/23/2014	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	1 kg
12/23/2014	AB-CHMINACA	San Francisco Intl Mail	China	Beaumont, TX	500 grams
12/31/2014	AB-CHMINACA	San Francisco Intl Mail	China	Beaumont, TX	600 grams
12/31/2014	AB-CHMINACA	San Francisco Intl Mail	China	McAllen, TX	1 kg
01/20/2015	AB-CHMINACA	San Francisco Intl Mail	China	Las Vegas, NV	3 kg
01/20/2015	AB-CHMINACA	San Francisco Intl Mail	China	Las Vegas, NV	2 kg
02/17/2015	AB-PINACA	San Francisco Intl Mail	China	Northridge, CA	unknown
03/9/2015	AB-CHMINACA	San Francisco Intl Mail	China	Fort Worth, TX	1 kg
03/9/2015	AB-PINACA	San Francisco Intl Mail	China	Houston, TX	1 kg
04/8/2015	AB-CHMINACA	San Francisco Intl Mail	China	Spokane, WA	100 grams

04/9/2015	AB-CHMINACA	San Francisco Intl Mail	China	Gainsville, GA	20 grams
04/15/2015	AB-CHMINACA	San Francisco Intl Mail	China	Albuquerque, NM	5 grams
04/29/2015	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	1 kg
05/5/2015	AB-CHMINACA	San Francisco Intl Mail	China	Richmond, TX	1 kg
05/5/2015	AB-CHMINACA	San Francisco Intl Mail	China	Bakersfield, CA	1 kg
05/5/2015	AB-CHMINACA	San Francisco Intl Mail	China	Bakersfield, CA	1 kg
05/5/2015	AB-CHMINACA	San Francisco Intl Mail	China	Bakersfield, CA	1 kg
05/27/2015	AB-CHMINACA	San Francisco Intl Mail	China	Houston, TX	1.5 kg