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)

Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5, and 6) for Temporary Scheduling

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Introduction

Recently, several synthetic cannabinoids (SCs) namely *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) emerged in the illicit drug market. In light of this, the Drug Enforcement Administration (DEA) reviewed the available scientific, medical, law enforcement and other data on these substances. The data presented in this document support the determination by the DEA to control these substances under the temporary scheduling provision of the Controlled Substances Act (CSA). 21 U.S.C. 811(h)(1).

SCs are substances synthesized in laboratories that mimic the biological effects of THC, the main psychoactive ingredient in marijuana. These chemicals, such as CP-47,497 and cannabicyclohexanol (designed in the 1980s and currently controlled), were initially used as research tools to investigate the biological mechanisms in the cannabinoid system and to develop novel therapies for various clinical conditions. Other SCs including JWH-018, JWH-073, and JWH-200 (all permanently controlled pursuant to the Food and Drug Administration Safety and Innovation Act. (FDASIA), Pub. L. 112-144) were synthesized in the mid-1990s and studied to further advance the understanding of drug-receptor interactions regarding the cannabinoid system.

SCs were first marketed in several European countries as herbal incense before the initial encounter in the United States by Customs and Border Protection (CBP) in November 2008. In 2009, their use began increasing in the United States with law

enforcement encounters describing SCs laced on plant material and being abused for their psychoactive properties. In addition, forensic analyses by the DEA and other Federal, State, and local laboratories have identified multiple variations in both the type and the amount of SC applied to the plant material.

As observed by the DEA and CBP, SCs originate from foreign sources, including China and other countries in Southeast Asia. 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. The powder form of SCs are typically dissolved in solvents (e.g., acetone) before being applied to a green plant material or dissolved in a propellant intended for use in e-cigarette devices. Law enforcement personnel have encountered various application methods including, buckets or cement mixers in which green plant material and one or more SCs are mixed together, as well as large areas where the green plant material is spread out so that a dissolved SC mixture can be applied directly. According to online discussion boards and law enforcement encounters, spraying or mixing the SCs on plant material provides a vehicle for the most common route of administration—smoking (using a pipe, a water pipe, or rolling the drug-spiked plant material in cigarette papers). Once mixed, the SC/green plant material is then allowed to dry before illicit manufacturers package the product for distribution, ignoring any control mechanisms to prevent contamination or to ensure a consistent, uniform concentration of the substance in each package. Adverse health consequences may also occur from directly ingesting the drug during the manufacturing process.

SCs are marketed under hundreds of different brand names, including “Spice,” “K2,” “Blaze,” “Red X Dawn,” “Paradise,” “Demon,” “Black Magic,” “Spike,” “Mr. Nice Guy,” “Ninja,” “Zohai,” “Yucatan,” “Fire,” “Crazy Clown,” “Mojo,” “Black Mamba,” “Black Voodoo,” “Scooby Snax,” “Bizzaro,” and many others. In addition, various “new generations” of SCs reflect the same or similar product labels while yielding a higher intensity and longer lasting highs, but with the user still being deprived of knowledge as to exactly what is contained inside the packaging.

The designer drug products laced with SCs are often sold under the guise of “herbal incense,” “potpourri,” etc., use various product names, and are routinely labeled “not for human consumption.” Additionally, these products are marketed as a “legal high” or “legal alternative to marijuana” and are readily available over the Internet, in head shops, or sold in convenience stores. There is an incorrect assumption

that these products are safe (Fattore and Fratta, 2011; McGuinness and Newell, 2012) and further, that mislabeling these products as "not for human consumption" is a legal defense to criminal prosecution.

These substances have no accepted medical use in the United States and have been reported to produce adverse health effects in humans while having a negative effect on communities. Acute and chronic abuse of SCs in general have been linked to adverse health effects including signs of addiction and withdrawal (Zimmermann et al., 2009; Muller et al., 2010; Nacca et al., 2013; Rominger et al., 2013), numerous reports of emergency room admissions resulting from their abuse (Forrester et al., 2011; Hermanns-Clausen et al., 2013; SAMHSA, 2012; Buser et al., 2014; Takematsu et al., 2014), overall toxicity (Gunderson et al., 2012; Hermanns-Clausen et al., 2013; Fantegrossi et al., 2014; Konstrand et al., 2013), and death (Behonick et al., 2014; Patton et al., 2013; Law Enforcement/Toxicology correspondence). Psychiatric case reports have been reported in the scientific literature detailing the harms of SC abuse and psychoses (Oluwabusi et al., 2012; Peglow et al., 2012; Thomas et al., 2012; Castellanos and Thorton, 2012; Papanti et al, 2013; Spaderna et al., 2013; Castaneto et al., 2014). The risk of adverse health effects is further increased by the fact that similar products vary in the composition and concentration of SCs applied on the plant material.

In March 2011, May 2013, and February 2014, the DEA emergency-scheduled multiple SCs to protect the public health and safety. They included JWH-018, JWH-073, JWH-200, CP-47,497, and CP-47,497 C8 (temporarily scheduled on March 1, 2011, at 76 FR 11075, and later placed in schedule I by section 1152 of FDASIA on July 9, 2012); UR-144, XLR11 and AKB48 (temporarily scheduled on May 16, 2013, at 78 FR 28735); and PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA (temporarily scheduled on February 10, 2014, at 79 FR 7577). Section 1152 of the FDASIA amended the Controlled Substances Act (CSA) by placing cannabimimetic agents and 26 specific substances (including 15 SCs, 2 synthetic cathinones, and 9 phenethylamines of the 2C-series) in schedule I. Although seizures of JWH-018, JWH-073, JWH-200, CP-47,497, and CP-47,497 C8 homologue showed a decline shortly after these drugs were scheduled, new SCs began to emerge on the designer drug market. A new generation of SCs, including UR-144, XLR11, and AKB48 quickly became the new drugs of choice in the synthetic marketplace. Following the temporary scheduling of UR-144, XLR11 and AKB48, the next generation of SCs quickly began emerging, which included PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA. More recently, law enforcement has been encountering yet another generation of SCs including *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).

AB-CHMINACA is a synthetic cannabinoid (figure 1) that has pharmacological effects similar to the schedule I hallucinogen delta-9-tetrahydrocannabinol (Δ9-THC) (RTI, 2014) and other temporarily and permanently controlled schedule I substances. AB-CHMINACA was not reported in the scientific literature prior to its appearance on the illicit drug market. According to the System to Retrieve Information from Drug Evidence (STRIDE[1]) data, there are 21 records for AB-CHMINACA from January 1, 2010, through September 30, 2014 (Query date: October 1, 2014). The National Forensic Laboratory Information System (NFLIS[2]) registered 586 reports containing AB-CHMINACA in 19 states from January 1, 2010, through November 25, 2014 (Query date: November 25, 2014). In addition, at least four deaths and multiple overdoses requiring emergency medical intervention have been reported involving the use of AB-CHMINACA (see Factor 6).

AB-PINACA is a synthetic cannabinoid (figure 1) that has pharmacological effects similar to the schedule I hallucinogen delta-9-tetrahydrocannabinol (Δ9-THC) (RTI, 2014) and other temporarily and permanently controlled schedule I substances. AB-PINACA first appeared in the scientific literature as a designer drug found in illegal products (Uchiyama et al., 2012). There are 245 records involving AB-PINACA in STRIDE from January 1, 2010, through September 30, 2014 (Query date: October 1, 2014). There are 3,783 reports in NFLIS from January 1, 2010, through November 25, 2014 (Query date: November 25, 2014) in 39 states. At least three deaths and multiple overdoses requiring emergency medical intervention have been reported involving the use of AB-PINACA (see Factor 6).

THJ-2201 is a synthetic cannabinoid (figure 1) that has pharmacological effects similar to the schedule I hallucinogen delta-9-tetrahydrocannabinol (Δ9-THC) (Janowsky, 2014) and other temporarily and permanently controlled schedule I substances. THJ-2201 was not reported in the scientific literature prior to its appearance on the illicit drug market. According to STRIDE data, there are 65 records for THJ-2201 from January 1, 2010, through September 30, 2014 (Query date: October 1, 2014). The National Forensic Laboratory Information System (NFLIS) registered 220 reports containing THJ-

[1] STRIDE is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from the DEA, other Federal agencies, and law enforcement agencies.
[2] NFLIS is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by state and local forensic laboratories in the United States.

2201 in 13 states from January 1, 2010, through September 30, 2014 (Query date: October 1, 2014).

With no approved medical use and with limited or no safety or toxicological information, these substances (AB-CHMINACA, AB-PINACA and THJ-2201) have emerged on the designer drug market and are being abused for their psychoactive properties. AB-CHMINACA, AB-PINACA and THJ-2201 were not included among the 15 SCs that are specifically named under FDASIA, and do not fall under the legal definition of cannabimimetic agents as provided under FDASIA. To protect the public health and safety, the DEA intends to temporarily place AB-CHMINACA, AB-PINACA and THJ-2201 in schedule I of the CSA. With respect to finding an imminent hazard to the public safety, the DEA has considered the factors required under the CSA for the temporary scheduling of AB-CHMINACA, AB-PINACA and THJ-2201. 21 U.S.C. 811(h)(3) and 811(c)(4)-(6).

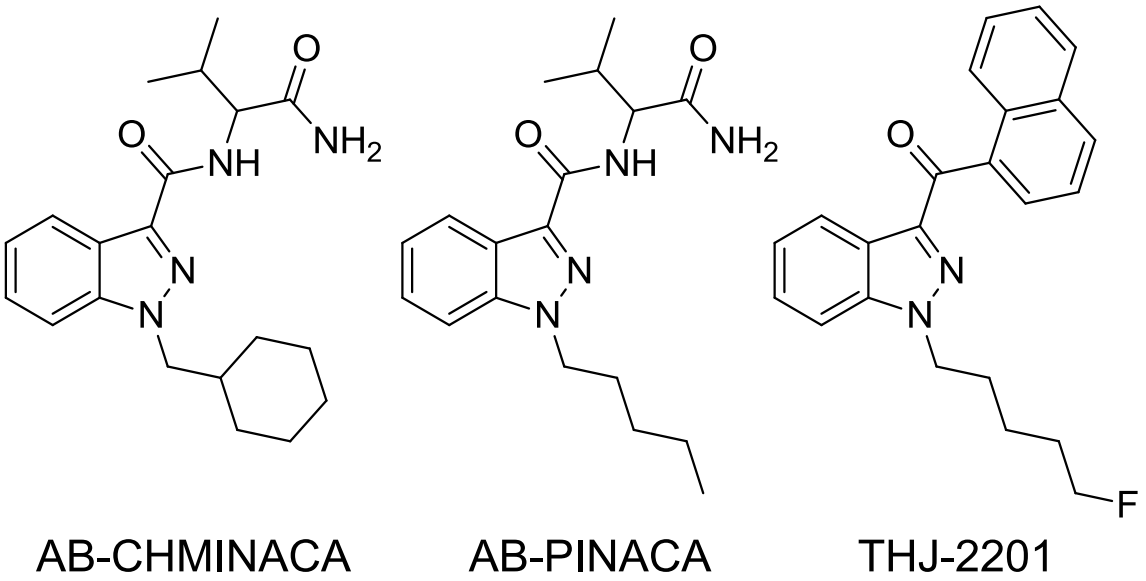

Figure 1. Chemical Structures

AB-CHMINACA, AB-PINACA, and THJ-2201 are classified as pentyl indazoles and share structural features with the schedule I substances AKB48 and AB-FUBINACA. AB-CHMINACA was not reported in the scientific literature prior to its emergence on the illicit drug market. AB-PINACA was first reported in the scientific literature following an extraction from “Fragrance Powder” purchased via the Internet in July 2012 (Uchiyama et al., 2013). Additionally, THJ-2201’s emergence on the illicit drug market preceded any report in the scientific literature.

Synthetic Cannabinoids

<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 have the same core structure where the 1- and 3-positions of the indazole ring system are substituted. 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 is substituted in both AB-CHMINACA and AB-FUBINACA. In AB-CHMINACA, the 1-position is substituted with a cyclohexylmethyl group, and in AB-FUBINACA, the 1-position of the indazole ring is substituted with a 4-fluorobenzyl group. A study conducted by contract researchers at RTI International indicated that AB-CHMINACA binds to the CB1 receptor (RTI, 2014).[3]

<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, where the 1- and 3-positions of the indazole ring system are substituted. All four of these substances are substituted at the 3-position with an amide. Like AB-CHMINACA and AB-FUBINACA, AB-PINACA is substituted at the amide nitrogen atom with the same 1-amino-3-methyl-1-oxobutan-2-yl group. AB-PINACA, like AKB48, contains a pentyl group on the indazole 1-position. Research has demonstrated that AB-PINACA binds to the CB1 receptor (RTI, 2014[4]; Prather, 2014) and is an agonist at the CB1 receptor.

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

THJ-2201 is also based on the same indazole core structure as AB-PINACA, AB-CHMINACA, AB-FUBINACA, and AKB48 where the 1- and 3-positions of the indazole ring system are substituted. These substitutions for THJ-2201 are the same substitutions as are found in AM-2201, where the core is indole. This single atom substitution from indole to indazole is the only difference between AM-2201 and THJ-2201. AM-2201 and

[3] Personal communication from RTI International to DEA, 09/08/2014.
[4] Personal communication from RTI International to ODEC, DEA, 09/08/2014.

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 AM-2201 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).

	In vitro	
	CB1 Binding Affinity (K_i)	**CB1 Functional Activity (EC_{50})**
AB-CHMINACA	0.74 nM[a]	TBD
AB-PINACA	2.64 nM[a]; 0.93 nM[c]	14.3 nM[c]
THJ-2201	10.3 nM[b]	1.05 nM[b]

[a] Correspondence from RTI International to DEA, 9/08/2014
[b] Janowsky, 2014
[c] Prather, 2014
TBD – to be determined

Table 1. *In vitro* data for AB-CHMINACA, AB-PINACA and THJ-2201

Factor 4. 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 reported in the United States in a November 2008 encounter, where a shipment of "Spice" was seized and analyzed by CBP 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 appears to have increased since January 2010 in the United States based on seizure evidence and public health and media reports.

Numerous SCs have been identified as product adulterants, and law enforcement has seized bulk powder of these substances. The first 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 FDASIA 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). Another generation of SCs including AB-CHMINACA, AB-PINACA and THJ-2201 has recently been encountered. These substances and laced 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 (CDC, 2013a, 2013b, 2013c; NFLIS, 2014; STRIDE, 2014).

Numerous herbal incense products have been found to contain one or more SC(s) laced on plant material (Appendix 2). 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 a euphoric and psychoactive "high," similar to marijuana (McKeever et al., 2014; Bonar et al., 2014). Data gathered from published studies, supplemented by discussions on Internet discussion websites and personal communications demonstrate that these products are being abused mainly by smoking for their psychoactive properties. The adulterated products 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 substances 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). This was reconfirmed in a recent publication analyzing various herbal products reporting that the green plant material found in SC products was devoid of psychoactive effects (Ogata et al., 2013) demonstrating that the effects observed following ingestion of a SC product originates from the actual SC, and not the plant material.

A major concern as reiterated by 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, all age groups have been reported by media as abusing these substances and related products. In 2010, an estimated 11,406 emergency department (ED) visits involved a synthetic cannabinoid product (SAMHSA, 2012). Three-fourths of these visits (75%) involved patients between the ages of 12-29. In addition, the majority (59%) of these emergency department visits of patients aged 12 to 29 did not involve any other substance. Of the remaining 41% of individuals, the most frequently abused substance in combination with SCs was marijuana (17%), pharmaceuticals (17%) and alcohol (13%) (SAMHSA, 2012). 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), 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 recent survey directed at patients seeking substance abuse disorder treatment reported multiple motives for use with the most commonly endorsed including 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). This data coincides with U.S. Drug Courts[5] 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).

The Monitoring the Future (MTF)[6] Report for 2012 detailed that while synthetic cannabinoid use, compared to 2011, has remained level in 12th graders at 11.3%, "the fact that its prevalence rate has remained high despite federal and state efforts to reduce its use is troublesome" (Johnston et al., 2013). Synthetic cannabinoid use in 8th and 10th graders was measured for the first time in 2012, with annual prevalence rates of 4.4% and

[5] 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.

[6] MTF is a national survey conducted by the Institute for Social Research at the University of Michigan under a grant from the NIDA that tracks drug use trends among American adolescents in the 8th, 10th, and 12th grades.

8.8%, respectively. The MTF Report for 2013 detailed that there was a significant decline in the use of SCs among 12th graders, decreasing from 11.3% in 2012 to 7.9% in 2013. Synthetic marijuana use decreased in the past year from 8.8% in 2012 to 7.4% in 2013 among 10th graders and from 4.4% to 4.0% among 8th graders (Johnston et al., 2014).

Dresen and colleagues (Dresen et al., 2010) found that SCs are being abused by individuals in drug treatment centers with a positive rate of 63.3% in forensic psychiatric centers based on their sampling. According to recent 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 cleanly passed a traditional drug screen tested positive for SCs.[7] The study continued 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 whether they had failed or passed a traditional drug screen.[8] In addition to the characterized psychoses, drivers with driving impairment have been encountered with confirmed presence of 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 opposing driver detected 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 Δ9-THC (Compton et al., 1992; Wiley et al., 1998; Weibelhaus 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 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).

As discussed previously, most users of SCs or SC-related products abuse these substances by smoking the product following application to plant material. Recently, law

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

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-FUBINACA, AB-CHMINACA, AB-PINACA, 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 ingesting a SC is viewed as being safer than traditional smoking (blunt, pipe, cigarette, etc.). In the study conducted by Bonar et al. (2014), while 91% of SC users reported ingesting 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. Similar to conventional illicit manufacturing of SC products, liquid preparations of these substances do not adhere to any manufacturing standards with regard to dosage, the substance(s) included, purity, or contamination. It is important to note that following manufacturing principles or standards would not eliminate the adverse effects observed with SC products and SCs would still be considered a threat to public safety.

The American Association of Poison Control Centers (AAPCC) reported a 219% increase from 2012 to 2013 in e-cigarette and liquid nicotine exposures (AAPCC, October 2014). Through October 31, 2014, the AAPCC has received 3,353 e-cigarette device and liquid nicotine exposures (table 2). As per the AAPCC, the term "exposure" means someone has had contact with the substance in some way; for example, ingested, inhaled, absorbed by the skin or eyes, etc. Not all exposures are poisonings or overdoses.

YEAR	# of Exposures
2011	271
2012	460
2013	1,542
2014*	3,353

Table 2. E-cigarette Device and Liquid Nicotine Reported Exposures to Poison Control Centers‡

‡ AAPCC, 2014

*Through October 31, 2014

<u>Summary</u>

Recently, law enforcement has been encountering AB-CHMINACA, AB-PINACA and THJ-2201 in increasing numbers. SCs and their associated products are available over the Internet or found to be sold in gas stations, convenience stores, and tobacco and head shops. AB-CHMINACA, AB-PINACA and THJ-2201, similar to the previously scheduled SCs (DEA, 2012; DEA, 2013; DEA, 2014), have been seized alone and/or spiked on products that are marketed as herbal incense and promoted as "legal" alternatives to marijuana.

Factor 5. The scope, duration, and significance of abuse

Following multiple scheduling actions in an attempt to safeguard the public from the adverse effects and safety issues associated with SCs, continued encounters by law enforcement and health care professionals are directly related to the increasing abuse of these substances and their associated products. With the passing of each Federal action, drug manufacturers and suppliers are adapting at an alarmingly quick pace to switch the ingredients to new, non-controlled variations of SCs. Emergency control of UR-144, XLR11, and AKB48 on May 16, 2013, resulted in an increase in the availability, trafficking and abuse of PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA. Emergency control of PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA on February 10, 2014, resulted in a similar pattern, with the emergence of AB-CHMINACA, AB-PINACA and THJ-2201.

Exposure incidents involving SCs continue to be documented by poison control centers in the United States as the abuse of these substances remains 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 3). Recently, AAPCC exposure reports are beginning to increase. The number of exposures reported demonstrates the dangerous health effects observed involving these chemicals. Exposures for August 2014 (442) were the highest received in a monthly period by the AAPCC since July 2012 (459) (AAPCC, October 2014). In addition, a majority of exposure incidents from 2012 to the present resulted in individuals seeking medical attention at health care facilities.[9]

[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 57 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).

YEAR	# OF CASES
2011	6,968
2012	5,230
2013	2,666
2014 (through October 31, 2014)	2,996

Table 3. Exposure cases of synthetic cannabinoids as reported to poison centers*

* AAPCC, October 31, 2014

Chronic abuse of SCs has been linked to signs of addiction and withdrawal similar to that experienced with cannabis abuse (Zimmermann et al., 2009; Muller et al., 2010; Vardakou et al., 2010). Tolerance to these drugs may develop fairly rapidly with larger doses being required to achieve the desired effect (EMCDDA, 2009). In 2010, the Substance Abuse and Mental Health Services Administration (SAMHSA) reported an estimated 11,406 emergency department visits involving a synthetic cannabinoid product. In 2011, SAMHSA reported the number of emergency department visits involving a synthetic cannabinoid product had increased significantly to an estimated 28,531 (SAMHSA, 2013) (figure 2).

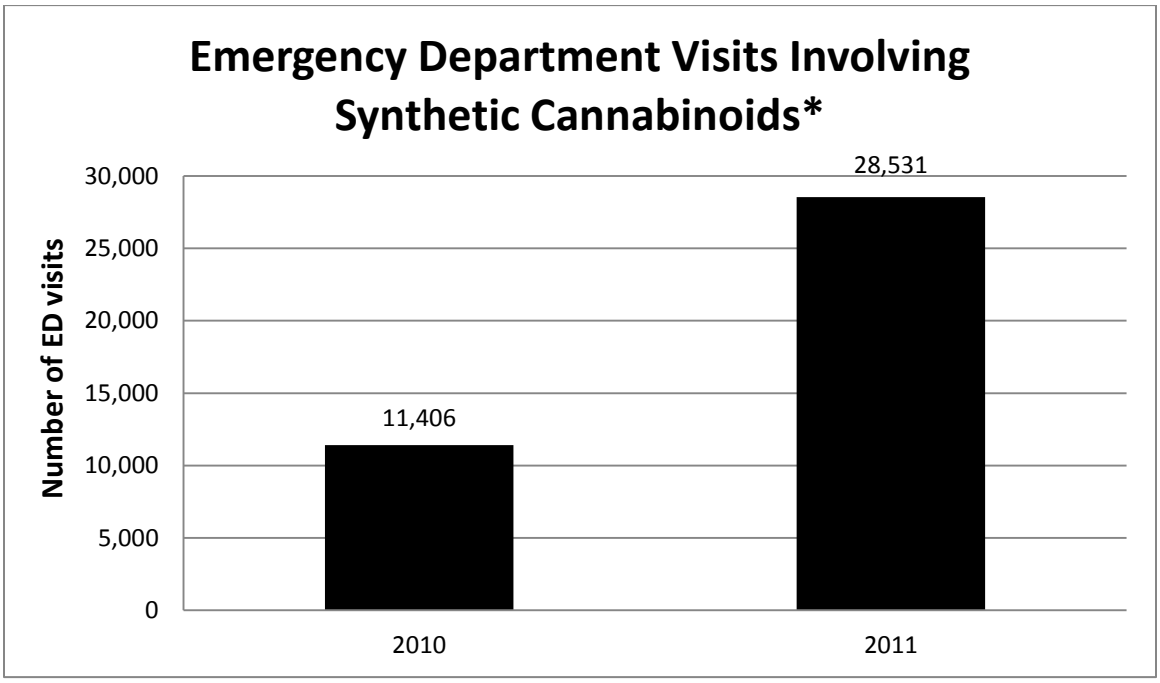

Figure 2. Emergency department visits involving synthetic cannabinoids (SAMHSA, 2013). Synthetic cannabinoid data were not reported prior to 2010.

*Estimates of ED visits are based on a representative sample of non-Federal, general, short-stay hospitals with 24-hour EDs in the United States.

The following tables (table 4; table 5) represent exhibits/reports obtained through both STRIDE and NFLIS that correspond to the specific drug listed. Additional information can be located in Appendix 1.

System to Retrieve Information from Drug Evidence (STRIDE)*		
DRUG	**EXHIBITS‡**	**DATES QUERIED**
AB-CHMINACA	21 (March 2014)	01/01/2010 – 09/30/2014
AB-PINACA	245 (June 2013)	01/01/2010 – 09/30/2014
THJ-2201	65 (September 2013)	01/01/2010 – 09/30/2014

Table 4. Reports obtained through the STRIDE database

* Query date: October 1, 2014

‡ The month in parenthesis (e.g., (March)) corresponds to the month the substance was first encountered

NFLIS*§			
DRUG	**2013 REPORTS‡**	**2014 REPORTS‡**	**STATES**
AB-CHMINACA	0	586 (February)	Arkansas, Arizona, California, Colorado, Georgia, Iowa, Indiana, Kansas, Kentucky, Louisiana, Missouri, North Dakota, New Jersey, Ohio, Oklahoma, Pennsylvania, Tennessee, Texas, Wisconsin
AB-PINACA	963 (March)	2,820	Alabama, Arkansas, Arizona, California, Colorado, Connecticut, Florida, Georgia, Iowa, Idaho, Illinois, Indiana, Kansas, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, Missouri, Mississippi, North Dakota, Nebraska, New Hampshire, New Jersey, Nevada, New York, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina,

			Tennessee, Texas, Utah, Virginia, Washington, Wisconsin, West Virginia, Wyoming
THJ-2201	0	220 (January)	Arkansas, Arizona, Connecticut, Georgia, Iowa, Illinois, Indiana, Kansas, Kentucky, Minnesota, Missouri, North Dakota, Nebraska, New Hampshire, New Jersey, Ohio, Pennsylvania, Tennessee, Wisconsin

Table 5. Reports obtained through the NFLIS database[§]

* Query date: November 25, 2014

‡ The month in parenthesis (e.g., (March)) corresponds to the month the substance was first encountered

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

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 products potentially laced with SCs that have resulted in visits to emergency departments. Following legislative control of JWH-018, JWH-200, JWH-073, CP-47,497, and cannabicyclohexanol, by FDASIA in July of 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

THJ-2201 was first observed in September 2013 while AB-CHMINACA was first observed in February of 2014. AB-PINACA has been for sale on the illicit drug market as early as March 2013. From December 2013 through September 2014, CBP reported select encounters of these substances with most shipments originating in China and intended for destinations within the United States: AB-CHMINACA–17 seizures involving 15.825 kg; AB-PINACA–4 seizures involving 6 kg; THJ-2201–6 seizures involving 5.5 kg (Appendix 2).[10] The

[10] Correspondence from CBP to DEA, (December 2013 – September 2014).

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).

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 and AB-PINACA. 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 male, Angola, Indiana; 37 year old male, Omaha, Nebraska) involving AB-PINACA. Cause of death in both cases were 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]
- 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 April 2014, a 52 year old male in Lafayette, Louisiana, suffered severe injuries after jumping through a window due to excited delirium following ingestion of a synthetic cannabinoid product “Mojo.” Laboratory results on drug evidence detected AB-CHMINACA.[16]
- 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.[17]

[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.
[14] STRIDE, DEA.
[15] Correspondence from AIT Laboratories to DEA, 08/07/2014.
[16] Correspondence from LA State Crime Lab to DEA, 05/01/2014.
[17] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.

- 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.[18]
- In May/June 2014, over 29 individuals in Gainesville, Florida, presented at local emergency departments while experiencing 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.[19]
- In June 2014, a 14 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.[20] [21]
- 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.[22]
- In June 2014, a 16 year old male and 17 year old female in Atlantic City, New Jersey, both experienced delirium after ingesting a liquid synthetic cannabinoid ingested through a hookah pen. Laboratory results on drug evidence detected AB-PINACA.[23]
- In June 2014, a 39 year old male in Baton Rouge, Louisiana, was transported by 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.[24]
- 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.[25] The cause of death as determined by the medical examiner was toxic effects of synthetic cannabinoid AB-CHMINACA.[26]
- In July 2014, a 10 month old infant in Shreveport, Louisiana, was admitted to the prenatal intensive care unit (PICU) following ingesting of a synthetic cannabinoid

[18] Report from the Office of the State Medical Examiner (OR) to DEA, 08/07/2014.
[19] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.
[20] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.
[21] Correspondence from Jefferson Parish Sheriff's Office to DEA, 07/10/2014.
[22] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.
[23] Correspondence from Atlantic City PD to DEA, 07/02/2014.
[24] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 07/24/2014.
[25] Correspondence from Orange County Crime Laboratory to DEA, 08/07/2014.
[26] Correspondence from Orange County Sheriff's Office to ODEC, DEA, 11/21/2014.

product. Laboratory analysis of drug evidence and biological samples detected AB-CHMINACA.[27]

- 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.[28]
- 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.[29]
- 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.[30]

Throughout 2013 and 2014, descriptions of overdoses, hospitalizations, severe outbreaks (CDC, 2013a,b,c) and deaths (Behonek et al., 2014) 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 safe due to the severe adverse effects associated with ingestion of illicit SCs. However, clinical effects 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 requiring medical intervention and 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). Specifically, 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, see Factor 6 list of OD/Death reports). A 12-month study conducted in 2012 demonstrated that out of 950 self-reported users, 2.4% reported having a medical emergency requiring treatment

[27] Correspondence from Shreveport, Louisiana PD to DEA, 10/07/2014.
[28] Correspondence from Franklin County Missouri Sheriff's Office to DEA, 08/26/2014.
[29] Correspondence from Dept. of Laboratory Medicine (UCSF) to DEA, 08/26/2014.
[30] Correspondence from Michigan State Police to DEA, 09/16/2014.

resulting from a combination of panic, anxiety, paranoia, and breathing difficulties (Winstock and Barratt, 2013). Data from this study also demonstrated that recent 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 figures reported by SAMSHA, which demonstrates that youth, specifically those aged 12 to 17 years old, comprise a large percentage of users requiring emergency medical attention (figure 3) (SAMSHA, 2012).

Since abusers obtain these drugs through unknown sources, the identity, purity, and quantity of these substances is uncertain and inconsistent, thus posing significant adverse health risks to users. The SCs encountered on the illicit drug market have no accepted medical use within the United States. Regardless, SC products continue to be easily available and abused by diverse populations. Unknown factors including 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 (Δ9-THC,JWH-018 and other temporarily and permanently controlled schedule I substances), SCs pose a risk to the abuser (Weissman et al., 1982; Compton et al., 1992; Wiley et al., 1998), and the chronic abuse of products laced with SCs has been linked to addiction and withdrawal (Vardakou et al., 2010).

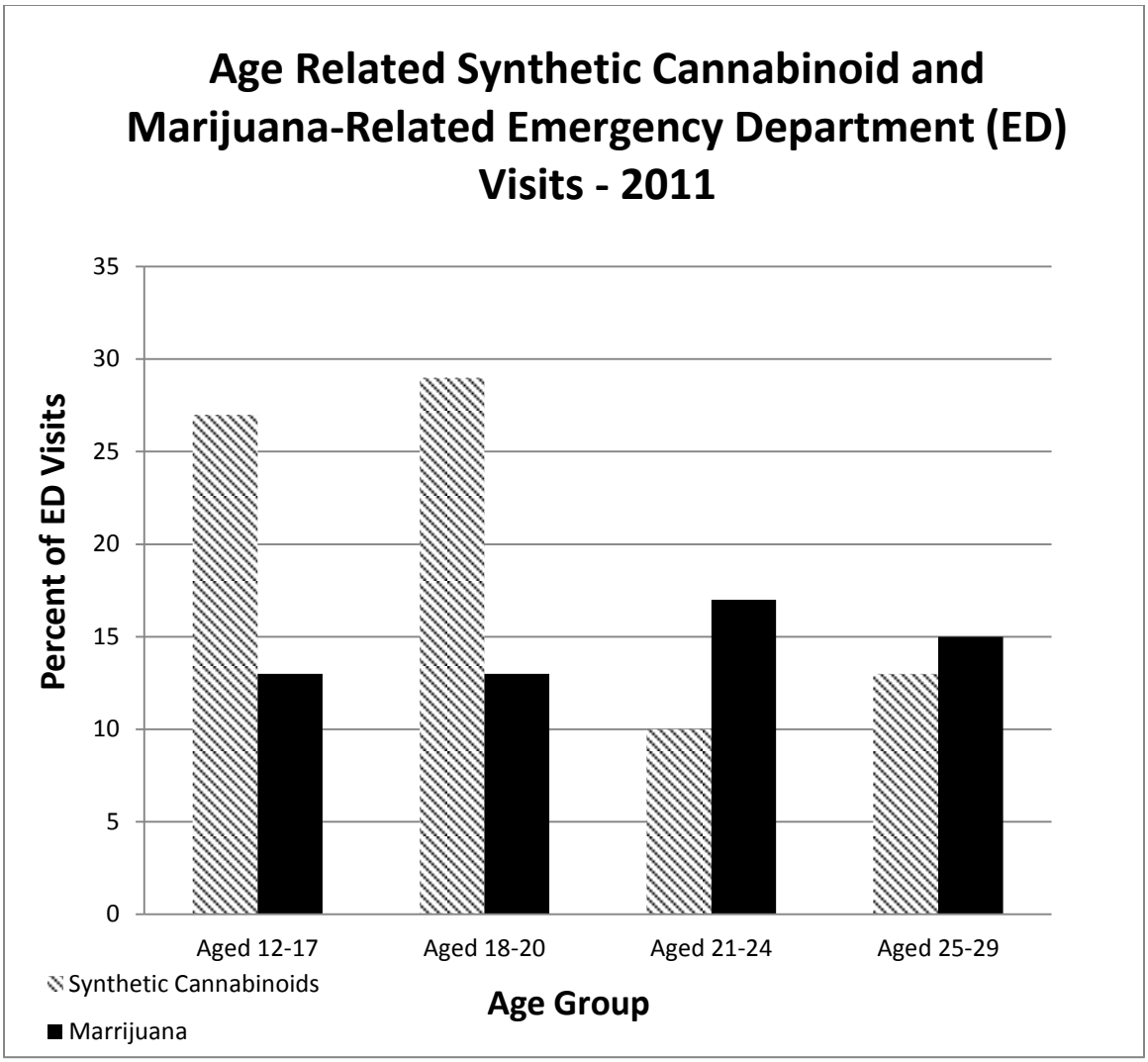

Figure 3. Age-related emergency department visits involving synthetic cannabinoids and marijuana (SAMHSA, 2014).

The CSA (21 U.S.C. 811(h)(4)) requires the Attorney General to notify the Secretary of the Department of Health and Human Services (HHS) of his intention to temporarily place a substance into schedule I of the CSA.[31] The Deputy Administrator transmitted notice of his intent to place AB-CHMINACA, AB-PINACA and THJ-2201 in schedule I on a temporary basis to the Assistant Secretary by letter dated September 17, 2014. The Assistant Secretary responded to this notice by letter dated September 30, 2014, and advised that based on review by the Food and Drug Administration (FDA), there are currently no approved new

[31] The Secretary of HHS has delegated to the Assistant Secretary for HHS the authority to make domestic drug scheduling recommendations. As set forth in a memorandum of understanding entered into by the HHS, the FDA, and NIDA, the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518.

drug applications or investigational new drug applications for AB-CHMINACA, AB-PINACA, or THJ-2201. The Assistant Secretary also stated that HHS has no objection to the temporary placement of AB-CHMINACA, AB-PINACA, and THJ-2201 into schedule I of the CSA. The DEA has taken into consideration the Assistant Secretary's comments. In accordance with 21 USC 811(h)(1), AB-CHMINACA, AB-PINACA, and THJ-2201 are not currently listed in any schedule under the CSA, and no exemptions or approvals are in effect for these substances under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). The DEA finds that the scheduling of AB-CHMINACA, AB-PINACA and THJ-2201 in schedule I on a temporary basis is necessary to avoid an imminent hazard to public safety and therefore intends to issue a temporary scheduling order. Any additional comments submitted by the Assistant Secretary in response to this notification shall also be taken into consideration before a final order is published. 21 U.S.C. 811(h)(4).

Conclusion of 3-Factor Analysis

After a careful review of the scientific literature, Factors 4, 5, and 6, NFLIS, STRIDE, and other law enforcement data and sources of information, it is evident that AB-CHMINACA, AB-PINACA, and THJ-2201 are trafficked and abused and pose an imminent hazard to public safety.

The DEA has considered the three criteria for placing a substance into schedule I of the CSA (21 U.S.C. 812). The data available and reviewed for AB-CHMINACA, AB-PINACA, and THJ-2201 indicated that these substances, including their salts, isomers, and salts of isomers, pose an imminent hazard to public safety and health, have high potential for abuse, have no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision.

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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.

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Appendix 1

Public Health

1. The Substance Abuse and Mental Health Services Administration (SAMHSA) reported that in 2010, an estimated 11,406 emergency department visits involved a synthetic cannabinoid product.
2. SAMHSA reported that in 2011, an estimated 28,531 emergency department visits involved a synthetic cannabinoid product, a significant increase over the 2010 estimated visits.
3. Monitoring the Future study results for 2012 (released 12/19/2012) state that for the second year of reporting, use of synthetic marijuana amongst 12th graders held level at 11.3%. Study authors stated that while a leveling was encouraging, the high prevalence rate despite Federal and State efforts to reduce its use was troublesome.
4. Monitoring the Future study results for 2013 (released 12/18/2013) state that use of synthetic marijuana amongst 12th graders fell from 11.3% in 2012 to 7.9% in 2013.
5. Health effects from the drug can be life-threatening and can include:
    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/
6. ...these substances are among the worst they have ever seen. People high on these drugs can get very agitated and violent, exhibit psychosis and severe behavior changes, and have harmed themselves and others. Some have been admitted to psychiatric hospitals and have experience continued neurological and psychological effects (News Release–American Association of Poison Control Centers: AAPCC Issues Statement on the Synthetic Drug Abuse Prevention Act, July 11, 2012).
7. 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)
8. At least 43 states have taken action to control one or more synthetic cannabinoids. (Office of National Drug Control Policy, 2014)
9. 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, 2014)

10. Spice abusers who have been taken to Poison Control Centers report symptoms that include rapid heart rate, vomiting, agitation, confusion, and hallucinations. Spice 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 heart attacks. Regular users may experience withdrawal and addiction symptoms. (National Institute on Drug Abuse, 2014)
11. In order to protect public health and well-being, Governor Maggie Hassan today declared a State of Emergency in the State of New Hampshire as a result of recent overdoses in Manchester and Concord as a result of the use or misuse of the synthetic cannabinoid identified as "Smacked!". (Press Release: Governor Hassan Declares State of Emergency as a Result of Overdoses from Synthetic Cannabinoid – August 14, 2014)
12. 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 an SC-containing product to avoid a positive drug test. The two most common reasons for SC use was "curiosity" (91%) and "to feel good or get high" (89%). (September, 2014)

Poison Control Centers

1. **March 24, 2010, AAPCC Press Release.** As of March 24, 2010, 112 exposure calls had been received since 2009 regarding synthetic cannabinoids and associated products, including 59 exposure calls since March 1, 2010, according to the National Poison Data System (NPDS).
2. **July 23, 2010, AAPCC Press Release.** As of July 23, 2010, 761 exposure calls had been received regarding synthetic cannabinoids and associated products according to NPDS.
3. **August 20, 2010, AAPCC Press Release.** As of August 20, 2010, 1,057 exposure calls had been received regarding synthetic cannabinoids and associated products according to NPDS.
4. **September 27, 2010, AAPCC Press Release.** As of September 27, 2010, 1,503 exposure calls had been received regarding synthetic cannabinoids and associated products according to NPDS.
5. **November 3, 2010, AAPCC Press Release.** As of November 3, 2010, 1,966 exposure calls have been received by poison centers regarding products purported to contain synthetic cannabinoids according to NPDS. Calls have been received in 48 states and the District of Columbia.

6. **November 22, 2010, AAPCC Press Release**. As of November 22, 2010, poison centers have reported 2,304 exposure calls regarding products purported to contain synthetic cannabinoids according to NPDS. Poison centers have received exposure calls in 49 states and the District of Columbia.
7. **December 21, 2010, AAPCC Press Release.** As of December 21, 2010, U.S. poison centers have reported receiving more than 2,500 exposure calls this year alone. As of December 21, 2010, poison centers have reported 2,752 exposure calls about the products according to NPDS.
8. **January 18, 2011, AAPCC Press Release.** As of January 18, 2011, U.S. poison centers have received more than 3,000 exposure calls regarding products purported to contain synthetic cannabinoids. In 2010, poison centers reported 2,867 exposure calls. As of January 18, 2011, U.S. poison centers have reported 217 exposure calls for 2011.
9. **February 3, 2011, AAPCC Press Release.** As of February 3, 2011, U.S. poison centers have reported 385 exposure calls for 2011.
10. **February 10, 2011, AAPCC Press Release.** Synthetic marijuana products have spurred more than 3,000 exposure calls to U.S. poison centers since 2010.
11. **February 24, 2011, AAPCC Press Release.** As of February 24, 2011, U.S. poison centers have reported 706 exposure calls for 2011. The total number of calls since 2010 is more than 3,500 exposure calls.
12. **April 20, 2011, AAPCC Press Release.** Synthetic marijuana products have spurred more than 4,500 exposure calls to U.S. poison control centers since 2010.
13. **July 11, 2012, AAPCC Press Release.** In 2010, poison centers nationwide responded to about 3,200 exposure calls related to synthetic marijuana and bath salts. In 2011, the number jumped to more than 13,000. Sixty percent of these cases involved patients 25 and younger.
14. **November 28, 2011, AAPCC Press Release.** Poison center data provides vital information leading to the DEA ban of synthetic drugs.
15. **February 16, 2012, AAPCC Press Release.** American Association of Poison Control Centers joins the Office of National Drug Control Policy Working Group in addressing the dangers of synthetic drugs.
16. **May 31, 2012, AAPCC Press Release.** The AAPCC commends the U.S. Senate for passing a ban of synthetic drugs in SB 3187 and call on the U.S. House of Representatives to include the language in the final version of the bill.
17. **July 11, 2012, AAPCC Press Release.** AAPCC comment the nation's policy makers on passage into the law the Synthetic Drug Abuse Prevention Act of 2012.

18. **From January 1, 2012 through December 31, 2012**, poison centers nationwide have received 5,230 exposure calls regarding exposure to synthetic cannabinoids.
19. **From January 1, 2013 through December, 2013**, poison centers nationwide have received 2,666 exposure calls regarding exposure to synthetic cannabinoids.
20. **From January 1, 2014 through October, 2014**, poison centers nationwide have received 2,996 exposure calls regarding exposure to synthetic cannabinoids.

Table 3. NFLIS – State and Local and other Federal Laboratory (not DEA) Forensic Laboratory Reports (Query date: November 25, 2014)

	2010				2011				2012				2013				2014			Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3‡	
JWH-018; JWH-073; JWH-200; CP-47,497 CP-47,497 C8 homologue	138	413	670	1,198	1,515	997	661	542	427	356	233	150	110	98	83	46	66	24	9	7,736
UR-144; XLR11; AKB48	1*	0	0	0	0	0	0	50	571	3,376	6,361	5,279	6,695	6,664	3,945	2,844	3,607	2,852	1,644	43,889
PB-22; 5F-PB-22; AB-FUBINACA; ADB-PINACA	0	0	0	0	0	0	0	0	0	0	1	0	356	1,017	2,066	2,361	3,262	2,408	1,055	12,526
AB-CHMINACA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	34	205	347	586
AB-PINACA	0	0	0	0	0	0	0	0	0	0	0	0	0	39	413	511	1,038	1,162	620	3,783
THJ-2201	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17	94	109	220

*Encounter confirmed in March 2012; ‡ = data are incomplete for third quarter 2014, still being reported.

Corresponds to the date substances were placed under temporary control

Table 4. STRIDE Records (January 1, 2010 through September 30, 2014) (Query date: October 1, 2014):

	NUMBER OF RECORDS
AB-CHMINACA	21
AB-PINACA	245
THJ-2201	65

Appendix 2

Table 5. Selected Reports from Customs and Border Protection Laboratory (December 2013 – September 2014)

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 Intl Mail	China	Baytown, TX	1 kg
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
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

Table 6. STRIDE Sample Laboratory Results

Date	Label	Flavor/ Characteristic	Confirmed Substance
6/26/2013	Diablo		AB-PINACA
6/26/2013	Dead Man Walking		AB-PINACA
6/26/2013	Joker		AB-PINACA
6/26/2013	Bizzaro		AB-PINACA
6/26/2013	Bling Monkey		AB-PINACA
7/15/2013	Funky Green Stuff		AB-PINACA
7/15/2013	LOL		AB-PINACA
7/15/2013	Out World		AB-PINACA
7/22/2013	3		AB-PINACA
7/22/2013	4-D		AB-PINACA
8/21/2013	Diablo		AB-PINACA
8/21/2013	Platinum		AB-PINACA
8/29/2013	Buddha Exotic Aroma		AB-PINACA
9/13/2013	Scooby Snax		AB-PINACA
10/25/2013	Bizzarro		AB-PINACA

10/25/2013	Ripped		AB-PINACA
11/7/2013	Scuby Snax		AB-PINACA
11/14/2013	The Hedgehog	Blueberry	AB-PINACA
11/15/2013	El Diablo		AB-PINACA
11/15/2013	Diesel		AB-PINACA
11/15/2013	Blackout		AB-PINACA
11/19/2013	Cloud XXX Car Freshener*	Coconut	AB-PINACA
11/21/2013	Mega Buzz		AB-PINACA
12/7/2013	Buddha Exotic Aroma		AB-PINACA
12/7/2013	Buddha Exotic Aroma	Coconut Twist	AB-PINACA
12/7/2013	Super Nova		AB-PINACA
12/10/2013	Super Nova		AB-PINACA
12/11/2013	Blackout		AB-PINACA
12/11/2013	El Diablo		AB-PINACA
12/11/2013	Red Bull		AB-PINACA
12/11/2013	Hawaiian Bliss		AB-PINACA
12/11/2013	Fist Pump		AB-PINACA
12/11/2013	Deadman		AB-PINACA
12/11/2013	Buddha Exotic Aroma	Sexy Strawberry	AB-PINACA
12/11/2013	Buddha Exotic Aroma	Coconut Twist	AB-PINACA
12/11/2013	Buddha Exotic Aroma		AB-PINACA
12/13/2013	Scooby Snax	Sour Apple	AB-PINACA
12/13/2013	XXX	Booty Licious Blue Barry	AB-PINACA
12/13/2013	Scooby Snax XXX Potpourri	Blueberry	AB-PINACA
12/13/2013	Scooby Snax Herbal Kush Potpourri	Pomegranate	AB-PINACA
12/13/2013	Scooby Snax Herbal Kush Potpourri	Strawberry	AB-PINACA
12/13/2013	Scooby Snax Herbal Kush Potpourri	Yum Yum	AB-PINACA
12/13/2013	XXX Rated Pussy Cat	Pomegranate	AB-PINACA
12/13/2013	XXX Rated	Sexy Strawberry	AB-PINACA
12/19/2013	Spice Gold		AB-PINACA
12/19/2013	Bizarro Original		AB-PINACA
12/19/2013	Black Mamba	Blueberry	AB-PINACA
1/9/2014	Histeria Black		AB-PINACA
1/9/2014	Game Over Potpourri		AB-PINACA
1/9/2014	Dr. Feelgood		AB-PINACA
1/14/2014	The Hedgehog	Blueberry	AB-PINACA
1/15/2014	Primo		AB-PINACA

1/15/2014	Platinum XXX		AB-PINACA
1/22/2014	Ocean Mist Scented Oil*		AB-PINACA
1/22/2014	Gypsy Moon*		AB-PINACA
1/31/2014	Original Potpourri	Knockout	AB-PINACA
1/31/2014	Scooby Snax	Kush	AB-PINACA
2/6/2014	Scooby Snax	Cherry	AB-PINACA
2/6/2014	Scooby Snax		AB-PINACA
2/6/2014	Knockout		AB-PINACA
2/12/2014	Scooby Snax		AB-PINACA
2/12/2014	Platinum XXX		AB-PINACA
2/12/2014	Black Diamond		AB-PINACA
2/12/2014	Black Diamond		AB-PINACA
2/12/2014	Get Real		AB-PINACA
2/12/2014	XXX Platinum		AB-PINACA
2/19/2014	Good Times*		AB-PINACA
2/19/2014	Tropical Rush*		AB-PINACA
3/6/2014	WTF	Watermelon	AB-PINACA
3/6/2014	Mad Hatter	Blueberry	AB-PINACA
3/7/2014	Autumn Air		THJ-2201
3/18/2014	Purefire		AB-PINACA
3/18/2014	King Kong		AB-PINACA
3/18/2014	California Dreams		THJ-2201
3/20/2014	Hulk'd Out Kitty		AB-CHMINACA
3/27/2014	Fragile: Feeling Easily Hurt		AB-PINACA
4/3/2014	Hookah Blast		THJ-2201
4/3/2014	Super Nova		THJ-2201
4/24/2014	Diablo		AB-CHMINACA
4/26/2014	Caution		AB-PINACA
4/29/2014	AK-47	24 Karat Gold	AB-PINACA
4/29/2014	Green Giant		AB-PINACA
4/29/2014	Smacked	Pineapple	AB-PINACA
4/29/2014	Smacked	Lemon Lime	AB-PINACA
4/30/2014	AK-47	24 Karat Gold	AB-PINACA
5/7/2014	Bomb! Marley	Blueberry	AB-CHMINACA
5/7/2014	OMG		THJ-2201
5/7/2014	AK-47	24 Karat Gold	THJ-2201
5/12/2014	7H		AB-PINACA
5/20/2014	Black Voodoo		AB-CHMINACA
5/27/2014	Scooby Snax	Strawberry	AB-CHMINACA

* Substance was identified in a liquid rather than being identified in a powder or applied to plant material.