U.S. Department of Justice

Drug Enforcement Administration

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)

Prepared by:
Office of Diversion Control, Drug and Chemical Evaluation Section
Washington, D.C. 20537

February 2012

I. Background

On March 1, 2011, the Administrator of the Drug Enforcement Administration (DEA) published a Final Order in the Federal Register temporarily placing five synthetic cannabinoids in Schedule I of the Controlled Substances Act (CSA) upon finding that these substances pose an imminent threat to public safety. 76 FR 11075. The five synthetic cannabinoids controlled are 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 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, CP-47,497 C8 homologue).

Numerous products, marketed under the guise of "herbal incense," with trade names such as "Spice" and "K2," have conclusively been found to contain these five substances. These products are manufactured by lacing plant material with the synthetic cannabinoids and marketed as "legal" alternatives to marijuana[1]. They are abused for their psychoactive properties and packaged with variable and unpredictable mixtures of one or more synthetic cannabinoids, with variable and unpredictable potency, and without any information as to the health and safety risks. The products containing these substances have no legitimate uses, while the substances contained within have no currently accepted medical use in treatment in the United States and have not been investigated for human use.

Aminoalkylindoles (AAIs) JWH-018, JWH-073, and JWH-200, and the cyclohexylphenols CP-47,497 and cannabicyclohexanol have been encountered alone and/or laced on plant material. Abuse of these substances is believed to be the result of their purported cannabimimetic properties and popular status as a "legal" alternative to marijuana (Schifano *et al.*, 2009; Lindigkeit *et al.*, 2009; Hudson and Ramsey, 2011). Since 2009, law enforcement encounters regarding these five substances have greatly increased in the United States. A limited number of clinical reports demonstrate addiction and withdrawal symptoms, general convulsions, cardiovascular toxicity, and psychosis associated with the abuse of herbal incense products containing these five synthetic cannabinoids. The laced synthetic cannabinoid, and not the plant material itself, is considered to be the pharmacologically active component in these products (Zuba *et al.*, 2011; Wells and Ott, 2011).

Numerous state public health and poison centers have warned of the dangers associated with the use of synthetic cannabinoids and their associated products being found on the designer drug market. In response to the abuse of these substances, as of January 13, 2012, forty-eight states in the U.S. have controlled at least one of these five synthetic cannabinoids. Numerous local jurisdictions have also placed controls on these designer drugs. Bans of the use of these synthetic cannabinoids by military personnel have also been issued in response to the abuse of these synthetic cannabinoids and the related products (Bebarta *et al.*, 2010; communications to DEA). Through December 31, 2011, the American Association of Poison Control Centers

[1] Note that ''marihuana'' is the spelling originally used in the Controlled Substances Act (CSA). This document uses the spelling that is more common in current usage, ''marijuana.''

(AAPCC) reported 9,922 [2]toxic exposure calls involving synthetic cannabinoids and its products, many of which were received en-route to or from emergency departments. Products containing at least one or more of the before-mentioned five synthetic cannabinoids have been connected to these exposure incidents.

Prior to the DEA Final Order published on March 1, 2011, the aforementioned substances and their associated products were, and still are, readily obtainable on Internet websites and in local retail shops (e.g., head shops, convenient stores, and tobacco shops). Even with no known legitimate use for these substances, law enforcement, including Customs and Border Protection, has had numerous encounters of bulk quantities (>10 g) of these substances. There have been reports of driving under the influence of these drugs (DUIDs) and jeopardizing the public safety. Additionally, law enforcement has uncovered product manufacturing labs of varying sizes. Law enforcement has encountered individuals abusing synthetic cannabinoids-containing products, driving under the influence of synthetic cannabinoids-containing products, manufacturing said products, and responding to exposure incidents that warrant admission of the users of these products to emergency departments. Accidental overdosing with complications is a public health concern. Additional health and safety concerns for the unsuspecting user are the lack of information regarding product ingredients and composition. Indeed, these herbal products laced with synthetic cannabinoids have been shown to vary largely in the amount and the particular synthetic cannabinoid(s) under the same retail product name (Auwärter *et al.*, 2009; Dresen *et al.*, 2010; Zuba *et al.*, 2011).

Pursuant to 21 U.S.C. 811(b) and after gathering the necessary data, on June 21, 2011, DEA requested from the Department of Health and Human Services (HHS) a scientific and medical evaluation and a scheduling recommendation for JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol. Pursuant to 21 U.S.C. 811 (b) and (c), on January 5, 2012, February 6, 2012, February 13, 2012, HHS provided DEA with the following scientific and medical evaluations: "Basis for the Recommendation to place 1-Pentyl-3-(1-naphtoyl)indole (JWH-018) and its Salts in Schedule I of the Controlled Substances Act (CSA)"; "Basis for the Recommendation to place Naphthalen-1-yl-(1-butylindole-3-yl)methanone (JWH-073) and its Salts in Schedule I of the Controlled Substances Act (CSA)"; "Basis for the Recommendation to place [1-[2-(4-Morpholinyl)ethyl]-1H-indol-3-yl]-1-naphthalenyl-methanone (JWH-200) and its Salts in Schedule I of the Controlled Substances Act (CSA)"; "Basis for the Recommendation to Place 5-(1,1- Dimethylheptyl)-2-[(1R,3S)-3-Hydroxycyclohexyl Phenol] and its Enantiomer 5-(1,1-Dimethylheptyl)-2-[(1S,3R)-3-Hydroxycyclohexyl Phenol](CP 47,497), and their Salts in Schedule I of the Controlled Substances Act (CSA)"; and "Basis for the Recommendation to Place Cannabicyclohexanol, (C8)-CP 47,497, Also Known as 5-(1,1- Dimethyloctyl)-2-[(1R,3S)-3-Hydroxycyclohexyl Phenol] and its Enantiomer 5-(1,1- Dimethyloctyl)-2-[(1S,3R)-3-Hydroxycyclohexyl Phenol], and its Salts in Schedule I of the Controlled Substances Act (CSA)." These evaluations then recommended, respectively, that JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol be added to Schedule I of the CSA.

[2] The figure "9,992" appearing at 77 FR 12512 should read "9,922."

The CSA requires DEA, as delegated by the Attorney General,[3] to determine whether HHS's scientific and medical evaluation and all other relevant data constitute substantial evidence of potential for abuse such that the substance should be scheduled. 21 U.S.C. 811(b).

[3] 28 CFR 0.100(b)

II. Eight Factors Determinative of Control

Pursuant to 21 U.S.C. 811(c), DEA must consider eight factors in making any finding of substantial evidence of potential for abuse, including the necessary data and law enforcement information relevant thereto.

Factor 1: Its Actual or Relative Potential for Abuse

Potential for Abuse

The abuse potential of the Schedule I cannabinoid delta-9-tetrahydrocannabinol (THC), the main active ingredient of marijuana, is well documented. The abuse of the five synthetic cannabinoids under evaluation is associated with their ability to evoke cannabinoid-like subjective effects similar to those evoked by THC.

a. Legislative History and Determination of Abuse Potential

The legislative history of the CSA provides four factors to consider in determining whether a particular drug or substance has potential for abuse:[4]

i. There is evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or
ii. There is significant diversion of the drug or substance from legitimate drug channels; or
iii. 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; or
iv. The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug or other substance will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant diversion 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.

i. Individuals are taking JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community

A number of case reports and case series have shown that individuals take these substances and products containing these substances in amounts sufficient to induce toxic effects similar to those induced by marijuana such as anxiety, tachycardia and hallucinations. Severe toxic effects including seizures, tachyarrhythmias and other cardiovascular toxicity, extreme anxiety leading to panic attacks and potentially suicide, and the precipitation or exacerbation of psychotic episodes have also been reported following abuse of these substances or products containing these substances (Lapoint *et al.*, 2011; Vandrey *et al.*, 2012; Simmons *et al.*, 2011a and b; Schneir and Baumhaeher, 2011). Further, law enforcement encounters suggest occurrences of fatal automotive accidents have been caused by drivers under the influence of products

[4] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); 1970 U.S.C.C.A.N. 4566, 4601.

containing synthetic cannabinoids, while one instance of a homicide perpetrated by an individual under the influence of JWH-018 has also been reported.

Because these substances act on the same molecular targets as the active ingredient of marijuana, THC, they are likely to share some of its harmful health effects. Briefly, Marijuana's potential harmful health effects include cardiovascular effects. Prenatal exposure to marijuana, and potentially to synthetic cannabinoids, can significantly impact the cognitive and behavioral development of children. Finally, it is now established that marijuana can cause psychological and physical dependence. Habitual marijuana users experience craving for the substance and abrupt abstinence from chronic marijuana smoking can produce withdrawal symptoms. Similarly, HHS states that case reports have demonstrated that herbal products containing synthetic cannabinoids produce physical dependence and a withdrawal syndrome (76 FR 40552, Zimmermann *et al.*, 2009).

ii. Significant diversion of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol from legitimate channels and/or ease with which drug can be obtained

Since March 1, 2011, JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have been temporarily controlled in Schedule I and have thus not been legally available unless for research purposes. Individuals, including minors, have been purchasing these substances from internet vendors, gas stations, convenience stores, and head shops, while other reports indicate U.S. military personnel have likewise been purchasing and abusing these substances. These substances and laced products are commonly marketed as "legal highs" and with a disclaimer "not for human consumption."

Additionally, large seizures of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have occurred by law enforcement. The National Forensic Laboratory Information System (NFLIS) details over 5,450 reports from state and local forensic laboratories identifying JWH-018, JWH-073, JWH-200, CP-47,497 or cannabicyclohexanol in drug related exhibits for a period from January 2009 to December 2011 from 39 states.

iii. Individuals are taking JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substance.

There is currently no accepted medical use for JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol, and no medical practitioner is currently licensed by law to administer them outside of an extremely limited research setting. Indeed, the FDA has not evaluated or approved a new drug application (NDA) for these synthetic cannabinoids for any therapeutic indication, and no investigational new drug (IND) application is currently active. According to the results of the 2011 Monitoring the Future survey of high schools students, 1 in 9 high school seniors (11.4%) have used "synthetic marijuana" (products often containing synthetic cannabinoids) in the past year (Johnston et al., 2012). It is one of the most frequently mentioned among high school seniors, second only to marijuana.

iv. JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol are so related in their action to a substance already listed as having a potential for abuse to make it likely that they will have the same potential 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 they have a substantial capability of creating hazards to the health of the user or to the safety of the community.

HHS states that JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol are potent cannabinoid receptor agonists with no antagonist activity and with abuse potential similar to the Schedule I substances marijuana and THC (the main psychoactive constituent of marijuana) (Wachtel et al., 2002). Two types of cannabinoid receptors, cannabinoid-1 (CB1) and cannabinoid-2 (CB2), have been characterized (Piomelli, 2005). These synthetic cannabinoids, similar to THC, have affinity for both CB1 and CB2 receptors. The cloning of cannabinoid receptors has verified the site of action of THC and other cannabinoids (Matsuda et al., 1990; Gerard et al., 1991). The CB1 receptors are thought to mediate the psychotropic effects of THC (Hanus et al., 1999).

HHS states that JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol appear to be marketed solely for abuse, for their cannabis-like activity and because, prior to March 1, 2011, they were not controlled under the CSA. Thus, commerce involving these synthetic cannabinoids is for the purpose of their abuse and to escape the regulatory and criminal penalties of the CSA. If uncontrolled, it is reasonable to assume there will be significant use of these synthetic cannabinoids contrary to, or without, medical advice, along with substantial hazards to the health of the user and to the safety of the community.

b. Actual or Relative Abuse Potential

Cannabicyclohexanol, CP-47,497, JWH-018, JWH-073, and JWH-200, similar to THC, are CB1 receptor agonists. The CB1 receptors are thought to be responsible for the euphoric and psychoactive effects of THC and related cannabinoids (Wells and Ott, 2011).

i. Animal Studies

Drug Discrimination Studies

The drug discrimination paradigm is used as an animal model of human subjective effects. This procedure provides a direct measure of stimulus specificity of a test drug in comparison with a known standard drug, or a neutral stimulus (e.g. injection of saline water). The light-headedness and warmth associated with having a few beers or the jitteriness and increased heart rate associated with drinking several cups of coffee are examples of substance-specific stimulus effects. The drug discrimination paradigm is based on the ability of nonhuman and human subjects to learn to identify the presence or absence of these stimuli and to differentiate among the constellation of stimuli produced by different pharmacological classes. In drug discrimination studies, the drug stimuli function as cues to guide behavioral choice, which is subsequently reinforced with food or money. Repeated pairing of the reinforcer with only drug-appropriate responses can engender reliable discrimination between drug and no-drug or amongst several drugs. Because some interoceptive stimuli are believed to be associated with the reinforcing effects of drugs, the drug discrimination paradigm is used to evaluate the abuse potential of new substances. In this procedure, animals are trained to recognize or discriminate the stimulus effects of a given dose of a particular training drug from those of (1) a different dose

of the same training drug, (2) a different training drug, or (3) saline/vehicle (i.e., a nondrug condition) (Compton *et al.*, 1993; Solinas *et al.*, 2006).

At the time of temporary scheduling of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol, DEA requested that the National Institute on Drug Abuse (NIDA) conduct pharmacological studies on these synthetic cannabinoids. The pharmacological studies conducted included animal drug discrimination studies on these substances (NIDA, 2011a,b, 2012a,b). The data from these studies as well as the data published in the scientific literature suggest that the discriminative stimulus effects of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol are similar to those of the Schedule I substance THC, the principal active constituent of marijuana. These data are discussed below.

JWH-018, JWH-200, JWH-073, and cannabicyclohexanol were tested for their ability to substitute for the discriminative stimulus effects of THC (3 mg/kg) in six male Sprague-Dawley rats using a two-lever choice methodology (NIDA, 2011a,b, 2012a,b). Food was available as a reinforcer under a fixed ratio 10 schedule when responding occurred on the injection appropriate lever. The substances or their vehicle [ethanol/Cremophor EL/0.9% saline (1:1:18) were administered as intraperitoneal injections. Dose ranges of 0.1 to 5 mg/kg for JWH-200, 0.03 to 1 mg/kg for JWH-018, 0.1 to 10 mg/kg for JWH-073 and 0.1 to 2.5 mg/kg for cannabicyclohexanol were examined.

JWH-200 substituted fully (ED50 = 1.16 mg/kg, 30 minutes before testing) for the discriminative stimulus effects produced by 3 mg/kg of THC. Response rate was decreased to 84% of vehicle control following 5 mg/kg JWH-200 (NIDA, 2011b).

JWH-018 substituted fully (ED50 = 0.39 mg/kg, 60 minutes before testing) for the discriminative stimulus effects produced by 3 mg/kg of THC. Response rate was decreased to 79% of vehicle control following 1 mg/kg JWH-018 (NIDA, 2011a).

JWH-073 substituted fully (ED50 = 0.88 mg/kg, 30 minutes before testing) for the discriminative stimulus effects produced by 3 mg/kg of THC. Response rate was decreased to 34% of vehicle control following 10 mg/kg JWH-073 (NIDA, 2012a).

Cannabicyclohexanol substituted fully (ED50 = 0.80 mg/kg, 30 minutes before testing) for the discriminative stimulus effects produced by 3 mg/kg of THC. Response rate was decreased to 51% of vehicle control following 2.5 mg/kg cannabicyclohexanol (NIDA, 2012b).

The above-mentioned data from the drug discrimination studies performed by the NIDA contract researchers are consistent with the several published reports on discriminative stimulus effects of these cannabinoids. These reports are described below.

Järbe and colleagues (2011) showed that JWH-018 (ED50 = 0.14 mg/kg, 30 minutes before testing and ED50 = 0.39 mg/kg, 90 minutes before testing) fully substitutes for THC in rats trained to discriminate the effects of vehicle from those produced by 3 mg/kg of THC. JWH-018 was about four-fold more potent than THC. The cannabinoid receptor 1-selective

antagonist/inverse agonist rimonabant produced surmountable blockade of the discriminative stimulus effects of both JWH-018 and THC.

Ginsberg and colleagues (2012) also showed that JWH-018 and JWH-073, similar to THC, produced THC-like drug appropriate responding in rhesus monkeys trained to discriminate THC (1 mg /kg i.v.) from saline. The ED50 values for JWH-018, JWH-073 and THC were 0.013, 0.058 and 0.044 mg/kg, respectively and the corresponding durations of actions were 2, 1 and 4 hours. Rimonabant, a CB1 receptor antagonist, upon pretreatment produced a surmountable antagonism of the discriminative stimulus effects JWH-018, JWH-073 and THC. Ginsberg and colleagues (2012) using monkeys discriminating the cannabinoid antagonist rimonabant (1 mg/kg, i.v.) during chronic THC (1 mg/kg/12 hours, s.c.) treatment, an assay sensitive to cannabinoid withdrawal, found that JWH-018 (0.32 – 3.2 mg/kg), JWH-073 (0.32-3.2 mg/kg) similar to THC (1-10 mg/kg), dose-dependently attenuated the rimonabant discriminative stimulus. Based on these data, these researchers concluded that JWH-018, JWH-073, and THC share a common receptor mechanism to produce THC-like subjective effects and to attenuate withdrawal effects of THC.

Weissman and colleagues (1982) showed that CP-47,497 fully substitutes for THC in animals trained to discriminate 3.2 mg/kg THC from its vehicle administered intraperitoneally. CP-47,497 (ED50 = 0.1 mg/kg, i.p. 60 minutes before testing) was about 6.8-fold more potent than THC (ED50 = 0.68 mg/kg, i.p.). These authors further showed that rats, upon subjecting to acquisition task for 56 days (trials) requiring discrimination between THC and CP-47,497, were unable to discriminate pharmacologically equivalent doses of these two substances. Thus these authors concluded that these two substances possess identical discriminative stimulus properties.

Similar to the present aminoalkylindoles (JWH-018, JWH-073 and JWH-200), and cyclohexanols (CP-47,497, and cannabicyclohexanol), various other substances of these two chemical classes aminoalkylindoles and cyclohexylphenols have also been shown to produce THC-like discriminative stimulus effects (Weissman *et al.*, 1982; Compton *et al.*, 1992a; Compton *et al.*, 1992b; Compton *et al.*, 1993; Wiley *et al.*, 1998; Vann *et al.*, 2009; Järbe *et al.*, 2010, 2011).

Cannabicyclohexanol, CP-47,497, JWH-018, JWH-073, and JWH-200 share pharmacological similarities with the Schedule I substance THC (Weissman *et al.*, 1982; Compton *et al.*, 1992a; Wiley *et al.*, 1998). Behavioral evaluations in animal models, especially drug discrimination studies suggest that aminoalkylindoles and cyclohexylphenols produce THC-like discriminative stimulus effects (Weissman *et al.*, 1982; Compton *et al.*, 1992a; Compton *et al.*, 1992b; Compton *et al.*, 1993; Wiley *et al.*, 1998; Järbe *et al.*, 2010). There are also numerous anecdotal self-reports substantiating that these substances and the associated products are abused by humans for their hallucinogenic effects, as well as, published reports indicating an increase in the abuse of these substances (Lindigkeit *et al.*, 2009; Every-Palmer *et al.*, 2011; AAPCC Press Releases). In evaluating symptoms upon smoking herbal incense products, Hermanns-Clausen and colleagues (2009) reported similarities between cases resembling severe cannabis-intoxication. Furthermore, the observed health effects are not anticipated based on the declared herbs (Auwärter *et al.*, 2009; Lindigkeit *et al.*, 2009; Zuba *et al.*, 2011; Ernst *et al.*, 2011). Tachyphylaxis has been described for the JWH-018 after

approximately three days of use, possibly attributable to receptor down-regulation (Wells and Ott, 2011).

The Mouse Tetrad Test

The mouse tetrad is a well-established paradigm for evaluating substances for cannabimimetic properties (Martin *et al.*, 1991). This tetrad includes pharmacological models that evaluate catalepsy, locomotor activity, hypothermia and antinociception in mice. JWH-018, JWH-200, CP-47,497 and cannabicyclohexanol were shown to be active in all four parameters of the mouse tetrad whereas JWH-073 was only tested, and shown to be active, in three of the four parameters of the tetrad test (Wiley *et al.*, 1998; Compton *et al.*, 1992b).

ii. Clinical studies and reports

Cannabicyclohexanol, CP-47,497, JWH-018, JWH-073, and JWH-200 have not been evaluated in human abuse liability studies. Furthermore, no studies have been undertaken to evaluate the toxicology and safety of these substances in humans.

An internet-based survey conducted with adults reporting at least one lifetime use of a "Spice" product, evaluated subjective effects of these synthetic cannabinoids were evaluated (Vandrey *et al.*, 2012). Most respondents (85%) indicated that Spice products produced subjective effects similar to cannabis, while fewer than 10% reported similarities between Spice products and other licit and illicit drugs. Despite producing effects similar to marijuana, 54% of respondents also reported Spice products produced subjective effects that were unique and discernible from other licit and illicit drugs. Authors stated that the frequency of hallucinations (28%) following Spice product use is also greater than what would be expected for cannabis consumption. Most respondents (87%) reported having a positive experience following use of a Spice product, though negative or unwanted effects following use were reported by 40% of the sample.

A case report from San Diego, CA, describes the presentation of two patients presented to the emergency department (ED) predominantly exhibiting anxiety after recreationally using a Spice product that was subsequently confirmed to contain the synthetic cannabinoids, JWH-018 and JWH-073 (Schneir *et al.*, 2011). One of the patients described feeling anxious, tremulous, and experiencing palpitations soon after using the product. Physical examination of one patient revealed normal vital signs, occasional inappropriate laughter, normal-sized pupils, bilaterally reddened conjunctiva, and a few beats of lateral gaze nystagmus bilaterally. The other patient displayed normal-sized pupils, bilaterally reddened conjunctiva, and tachycardia.

A recent case report by Schneir and Baumhaeher (2011) describes a 19-year-old male patient who had two witnessed generalized convulsions soon after smoking a Spice product that was later confirmed to contain JWH- 018 and three other different synthetic cannabinoids (JWH-081, JWH-250, and AM-2201). Convulsions have been described in another published report for which there was no laboratory confirmation for the presence of synthetic cannabinoids (Simmons *et al.*, 2011a). In another report, in which there was laboratory confirmation for metabolites of the synthetic cannabinoid JWH-018, a patient was interpreted by the authors as having had a possible convulsion (Simmons *et al.*, 2011b).

c. Actual Abuse

As of January 13, 2012, forty-eight states in the U.S. have controlled at least one of these five synthetic cannabinoids. Numerous local jurisdictions have also placed controls on these designer drugs. Bans of the use of these synthetic cannabinoids by military personnel have also been issued in response to the abuse of these synthetic cannabinoids and their related products (Bebarta *et al.*, 2010; communications to DEA). These substances have been developed over the last 30 years to investigate their cannabimimetic properties. Subsequently, these substances have been identified as ingredients in numerous retail products (Auwärter *et al.*, 2009; Zuba *et al.*, 2009; Hudson *et al.*, 2010; Uchiyama *et al.*, 2010a,b, 2011; Dresen *et al.*, 2010; EMCCDA, 2009). JWH-018 was the first synthetic cannabinoid to be identified as a product ingredient in Germany in 2008.

Forensic Laboratory Data

The National Forensic Laboratory Information System (NFLIS) is a program sponsored by DEA's Office of Diversion Control. NFLIS compiles information on exhibits analyzed in state and local law enforcement laboratories. The System to Retrieve Information from Drug Evidence (STRIDE) is a DEA database which compiles information on exhibits analyzed in DEA laboratories. NFLIS and STRIDE together capture data for all substances reported by forensic laboratory analyses. More than 1,700 unique substances are reported to these two databases.

Large seizures of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have occurred by law enforcement. NFLIS details over 5,450 reports from state and local forensic laboratories identifying JWH-018, JWH-073, JWH-200, CP-47,497 and/or cannabicyclohexanol in drug related exhibits for a period from January 2009 to December 2011 from 39 States (Table 1).

Table 1. *Selected Synthetic Cannabinoids Number of Exhibits (State and Local Labs) in NFLIS (January 2009 - December 2011)*

	2009	**2010**	**2011**	**Drug Totals**
1-Pentyl-3-(1-naphtoyl)indole (JWH-018)	**19**	**2,013**	**2,598**	**4,630**
1-Butyl-3-(1-naphthoyl)indole (JWH-073)	**2**	**298**	**407**	**707**
1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200)	**0**	**61**	**41**	**102**
5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497)	0	0	3	**3**
Cannabicyclohexanol	0	5	5	**10**
	21	**2,377**	**3,054**	**5,452**
NFLIS database queried 02-21-2012. State and Local Forensic Laboratory drug reports				**TOTALS**
First, second and third drug reports analyzed, by submission date.				
Drugs reported to NFLIS in December 2011 are likely incomplete as of February 21, 2012, due to laboratory reporting lag time.				

STRIDE also details reports from federal forensic laboratories identifying JWH-018, JWH-073, and JWH-200 in drug related exhibits for a period from January 2009 to December 2011 (Table 2).

Table 2. *Selected Synthetic Cannabinoids Number of Exhibits (Federal Labs) in STRIDE (January 2009 - December 2011).*

	2009	**2010**	**2011**	**Drug Totals**
1-Pentyl-3-(1-naphtoyl)indole (JWH-018)	**4**	**48**	**149**	**201**
1-Butyl-3-(1-naphthoyl)indole (JWH-073)	**1**	**6**	**59**	**66**
1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200)	**0**	**0**	**6**	**6**
5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497)	**0**	**0**	**0**	**0**
Cannabicyclohexanol	**0**	**0**	**0**	**0**
	5	**54**	**214**	**273**
STRIDE database queried 02-21-2012. Federal Forensic Laboratory drug reports				**TOTALS**
All drug reports analyzed, by submission date				

According to the results of the 2011 Monitoring the Future survey of high schools students, 1 in 9 high school seniors (11.4%) have used synthetic marijuana in the past year (Johnston et al., 2012). It is one of the most frequently mentioned among high school seniors in this survey, second only to marijuana.

State public health and poison centers have issued warnings in response to adverse health effects associated with herbal incense products containing synthetic cannabinoids. These effects included tachycardia, elevated blood pressure, unconsciousness, tremors, seizures, vomiting, hallucinations, agitation, anxiety, pallor, numbness and tingling. Scientific literature reports by emergency department physicians and toxicologists have been published which characterize the abuse of JWH-018 (Vearrier and Osterhoudt, 2010; Canning *et al.*, 2010; Schneir *et al.*, 2011; Banerji *et al.*, 2010; Hermanns-Clausen *et al.*, 2009). Additionally, numerous public health and poison centers have issued warnings regarding the abuse of synthetic cannabinoids and the associated products. Bans of the use of these synthetic cannabinoids by military personnel have been issued in response to the abuse of synthetic cannabinoids and the related products (Bebarta *et al.*, 2010; communications to DEA).

Dresen and colleagues (2011) analyzed 101 serum samples from 80 subjects provided by different hospitals, detoxification and therapy centers, forensic psychiatry centers, and Institutes of Forensic Medicine. The prevalence of positive samples for the presence of cannabinoids of the aminoalkyindole type was highest amongst those originating from forensic psychiatric centers, 63.3% positive samples (Dresen *et al.*, 2011). Additionally, U.S. Drug Courts have communicated concerns related to the abuse of synthetic cannabinoids and provided DEA with data demonstrating a response rate of greater than 30% by juveniles subject to routine drug screens. Both reports suggest drug replacement in treatment settings.

HHS states in their recommendations to place JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol in Schedule I of the CSA that these substances are cannabinoid agonists. HHS also states that based on their pharmacological similarity to THC, it is reasonable to assume JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol will have a potential for abuse that is similar to that of marijuana and THC (both in Schedule I). Although these substances were originally developed as legitimate research tools, HHS is unaware of any legitimate commercial uses of JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol. HHS believes that JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol are marketed solely for abuse because the substances elicits cannabis-like activity and are not controlled under the CSA. Thus, commerce involving JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol is for the purpose of their abuse and to escape the regulatory and criminal penalties of the CSA. If uncontrolled, it is reasonable to assume that there will be significant use of JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol contrary to or without medical advice, and substantial hazards to the health of the user or to the safety of the community.

Factor 2: Scientific Evidence of its Pharmacological Effect, if Known

The aminoalkylindoles JWH-018, JWH-073, and JWH-200 were developed as research tools to investigate the CB1 and CB2 receptors (Pacheco *et al.*, 1991; Huffman *et al.*, 1994; Wiley *et al.*, 1998). In addition to binding studies, JWH-018 and JWH-200 have been evaluated in functional assays and behavioral studies (Pacheco *et al.*, 1991; Bell *et al.*, 1991; Eissenstat *et al.*, 1995; Wiley *et al.*, 1998; Atwood *et al.*, 2010). The cyclohexylphenols CP-47,497 and cannabicyclohexanol have been evaluated in binding and behavioral studies (Weissman *et al.*, 1982; Melvin *et al.*, 1984; Compton *et al.*, 1993; Atwood *et al.*, 2011), while CP-47,497 has also been evaluated in drug discrimination studies (Weissman *et al.*, 1982).

HHS states in their recommendations to place JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol in Schedule I of the CSA that *in vitro* and preclinical studies suggest that the pharmacological effects of JWH-018, JWH-073, JWH-200 CP-47,497 and cannabicyclohexanol are similar to those of THC.

Receptor Binding Profile

Homogenates of rat brain cortices for CB1 receptor binding were used to examine JWH-018 and JWH-073's binding to cannabinoid receptors (Aung *et al.*, 2000). JWH-018 (Ki = 9.0 +/- 5.00 nM) and JWH-073 (Ki = 8.9 +/- 1.8 nM) bind with high affinity to the central CB1 receptor, with higher affinity than THC (CB1 Ki = 40.7 +/- 1.7 nM) (Aung *et al.*, 2000).

According to HHS, NIDA studies showed that JWH-200 had a Ki of 134.0 nM at the CB1 receptor, and a Ki of 20.5 nM at the CB2 receptors. Similarly several other published reports indicate that JWH-200 bind to CB1 receptors with a relatively high affinity (Eissenstat et al., 1995; Huffman et al., 2003; Yamada et al., 1996).

In rat cortical membranes, using displacement of tritiated CP-55,940, cannabicyclohexanol and CP-47,497 were found to bind to the CB1 receptor with affinities of 4.73 +/- 1.34 and 9.54 +/- 0.35 nM, respectively, compared to THC's lower affinity of 40.7 +/- 1.7 nM (Compton *et al.*, 1993). In similar preparations, JWH-200 was found to bind to the CB1 receptor with an affinity of 42 +/- 5 nM (Huffman *et al.*, 2003).

Receptor Activation

In cultured HEK293 cells, JWH-018 increased ERK ½ MAPK phosphorylation and induced CB1 receptor internalization. These results indicate that JWH-018 behaves as a agonist at the CB1 receptor (Atwood *et al.*, 2010). JWH-018 was also shown to inhibit forsklin-stimulated cAMP production (Chin *et al.*, 1999).

According to HHS, NIDA studies using a CB1 agonist functional assay, showed that JWH-073 has agonist activity with an EC50 of 164 nM and an average maximal response of 56.3% of that of the reference CB1 agonist, WIN 55,212-2. Similarly, JWH-073 had an EC50 of 104.8 nM in another functional assay of cannabinoid receptor activation using [^{35}S]GTPγS in rat cerebellar membranes (Griffin et al., 1998).

According to HHS, NIDA studies using a CB1 agonist functional assay showed agonist activity of JWH-200 at the CB1 receptor with an EC50 of 305.5 nM and an average maximal response of 75.4% relative to the reference CB1 agonist, WIN 55,212-2 (NIDA, personal communication).

According to HHS, NIDA studies using CB1 agonist functional assay showed that cannabicyclohexanol has agonist activity at the CB1 receptor with an EC50 of 52.7 nM and an average maximum response of 90.47% of that of the reference CB1 agonist WIN 55,212-2 (NIDA, personal communication).

HHS states that inhibition of contractions of rodent vas deferens tissue occurs after treatment with THC, and is an *in vitro* assay used to assess CB1 receptor agonist activity (Christopoulos et al., 2002; Pertwee et al., 1992). JWH-200 was found to inhibit electrically evoked contractions in the mouse vas deferens assay (Eissenstat et al., 1995; Bell et al., 1991). It has been established that the potencies of aminoalkylindole agonists required to inhibit smooth muscle contraction in vitro correlated with their antinociceptive potency, as measured by both acetylcholine (Ach) and acetic acid-induced writhing assays (Ward *et al.*, 1990).

Cannabicyclohexanol and JWH-073 were shown to induce CB1 internalization (Atwood *et al.*, 2011). JWH-200 and CP-47,497 caused G-protein-dependent inhibition of adenylyl cyclase in rat striatum and cerebellum membranes (Pacheco *et al.*, 1991; Howlett et al., 1988), consistent with CB1 receptor signal transduction (Turu and Hunyady, 2010) and CB1 receptor brain localization (Mackie, 2005).

Animal Studies – Behavioral Effects

The mouse tetrad is a well-established paradigm for evaluating substances for cannabimimetic properties (Martin *et al.*, 1991). This tetrad includes pharmacological models that evaluate catalepsy, locomotor activity, hypothermia and antinociception in mice. JWH-018, JWH-200, CP-47,497 and cannabicyclohexanol were shown to be active in all four parameters of the mouse tetrad whereas JWH-073 was only tested, and shown to be active, in three of the four parameters of the tetrad test (Wiley *et al.*, 1998; Compton *et al.*, 1992b).

Cannabinoid drug discrimination studies are an accepted animal model for predicting subjective effects in humans (Balster and Prescott, 1992), and drug discrimination data is presented for all five substances under Factor 1. Briefly, all five substances were found to substitute fully for THC, suggesting their subjective effects would be similar to those of THC.

Cytotoxic Effects

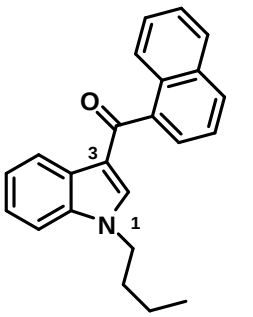
CP-47,497 and cannabicyclohexanol were found to be cytotoxic towards NG 108-15 cells (Tomiyama and Funada, 2011). Their findings suggest that caspase-cascades may play an important role in the apoptosis induced by these two cannabinoids.

Factor 3: The State of Current Scientific Knowledge Regarding the Drug or Other Substances

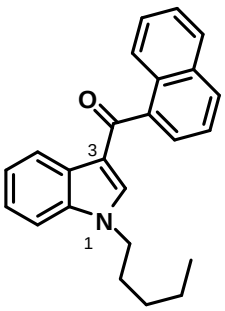
The cyclohexylphenols CP-47,497 and cannabicyclohexanol (CP-47,497-C8 homologue) were designed to investigate SAR based on the potent substance, 9-nor-9β-hydroxyhexahydrocannabinol (HHC) (Weissman *et al.*, 1982; Melvin *et al.*, 1984). Interest in AAI structural class was generated by the mouse vas deferens and prostaglandin synthetase activity of pravadoline and subsequent finding that AAIs bind to the cannabinoid receptor (Huffman, 2009). The pharmacophoric model for AAI binding at the CB1 was first introduced by Eissenstat and colleagues (1991). The aminoalklylindoles with affinity for CB1 are structurally based on a central indole ring substituted at the 1-and 3-positions, with a possible 2-position methyl group. JWH-200 was investigated based on structural similarities to the extensively studied substance WIN-55,212-2. Further structural modifications at the 1-position gave JWH-018 and JWH-073. These substances have been termed 'synthetic' or 'non-classical' due to activity at the CB1 and CB2 while being structurally distinct from naturally occurring cannabinoids.

The appearance of these substances in the designer drug market can be traced to the initial forensic laboratory confirmation in mid-December 2008. A commercial laboratory in Frankfurt, Germany announced the identification of JWH-018 in samples of herbal incense and others were identified shortly after this initial determination (Piggee, 2009).

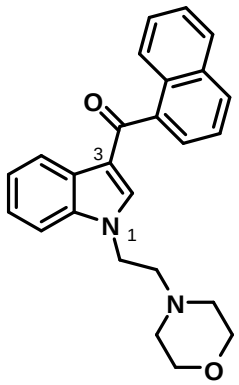
Chemistry and Physical Properties



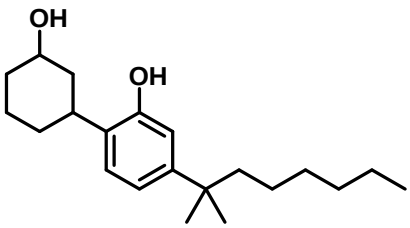
1-butyl-3-(1-naphthoyl)indole



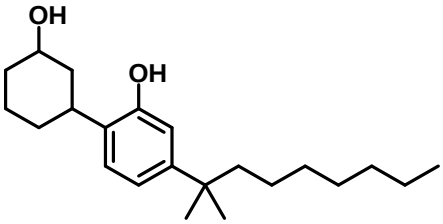
1-pentyl-3-(1-naphthoyl)indole



1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole



5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol



5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol

Table 3. *The chemical and physical properties of 1-butyl-3-(1-naphthoyl)indole*

1-butyl-3-(1-naphthoyl)indole	
CAS #	208987-48-8
Chemical Formula	$C_{23}H_{21}NO$
Molecular Weight	327.42
Synonyms	JWH-073
Systemic Name (IUPAC, CAS)	naphthalen-1-yl-(1-butyl-1*H*-indol-3-yl)methanone

Table 4. *The chemical and physical properties of 1-pentyl-3-(1-naphthoyl)indole*

1-pentyl-3-(1-naphthoyl)indole	
CAS #	209414-07-3
Chemical Formula	$C_{24}H_{23}NO$
Molecular Weight	341.45
Synonyms	JWH-018; AM678
Systemic Name (IUPAC, CAS)	naphthalen-1-yl-(1-pentyl-1*H*-indol-3-yl)methanone

Table 5. *The chemical and physical properties of 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole*

1-[2-(4-morpholinyl)ethyl-3-(1-naphthoyl)indole	
CAS #	103610-04-4
Chemical Formula	$C_{25}H_{24}N_2O_2$
Molecular Weight	384.47
Synonyms	JWH-200
Systemic Name (IUPAC, CAS)	(1-(2-morpholinoethyl)-1H-indol-3-yl)(naphthalene-1-yl)methanone
Melting Point	104-106^{0}C (Bell *et al.*, 1991)

Table 6. *The chemical and physical properties of 5-(1,1-dimethylheptyl)-2-[3-hydroxycyclohexyl]-phenol*

5-(1,1-dimethylheptyl)-2-[(1*R*,3*S*)-3-hydroxycyclohexyl]-phenol	
CAS #	114753-51-4, (-)-CP-47,497; 70434-82-1, (±)-CP-47,497
Chemical Formula	$C_{21}H_{34}O_2$
Molecular Weight	318.49
Synonyms	CP-47,497
Systemic Name (IUPAC, CAS)	2-(hydroxycyclohexyl)-5-(2-methyloctan-2-yl)phenol
Appearance	solid

Table 7. *The chemical and physical properties of 5-(1,1-dimethyloctyl)-2-[3-hydroxycyclohexyl]-phenol*

5-(1,1-dimethyloctyl)-2-[(1*R*,3*S*)-3-hydroxycyclohexyl]-phenol	
CAS #	70434-92-3, (±)-CP-47,497 C8 homologue
Chemical Formula	$C_{22}H_{36}O_2$
Molecular Weight	332.52
Synonyms	Cannabicyclohexanol; CP-47,497 C8 homologue
Systemic Name (IUPAC, CAS)	2-3-hydroxycyclohexyl)-5-(2-methylnonan-2-yl)phenol
Appearance	solid

Laboratory analyses of numerous herbal incense products have been conducted and results have been published in the scientific literature detailing the identification of these synthetic cannabinoids in products and the variations in the amount of the substance laced on the plant material in products sold through retail channels (Auwärter *et al.*, 2009; EMCDDA, 2009; Dresen *et al.*, 2010; Uchiyama *et al.*, 2010a,b, 2011; Hudson *et al.*, 2010; Zuba *et al.*, 2011).

Metabolism and Pharmacokinetics

Metabolism studies have been conducted for JWH-018 (Teske *et al.*, 2010; Sobolevsky *et al.*, 2010; Wintermeyer *et al.*, 2010; Möller *et al.*, 2011) and JWH-073 (Chimalakonda *et al.*, 2011; Grigoryev *et al.*, 2011; Moran *et al.*, 2011; Hutter *et al.*, 2012), as well as for CP-47,497 (Dowling and Regan, 2011; Dresen *et al.*, 2011).

Brents and colleagues reported *in vitro* and *in vivo* activities for JWH-018 metabolites (Brents *et al.*, 2011). These results prompted other researchers to suggest that these active metabolites in conjunction with higher CB1 receptor activity relative to THC may contribute to a greater prevalence of adverse health effects (Fattore and Fratta, 2011).

Medical Application

DEA is not aware of any currently accepted medical use for cannabicyclohexanol, CP-47,497, JWH-018, JWH-073, or JWH-200. A letter dated October 6, 2010 was sent from the DEA Deputy Administrator to the Assistant Secretary for Health of HHS as notification of intent to temporarily place these five substances in Schedule I. DEA solicited comments from HHS, including whether there is an exemption or approval in effect for the substances in question under the Federal Food, Drug and Cosmetic Act. In a letter to the DEA Acting Administrator dated November 22, 2010, the Assistant Secretary of Health responded that there were no current INDs or NDAs for these synthetic cannabinoids.

Factor 4: Its History and Current Pattern of Abuse

Synthetic cannabinoids have been developed over the last 30 years to investigate their cannabimimetic properties and as research tools to investigate the cannabinoid systems (Huffman *et al.*, 1994; Wiley *et al.*, 1998). Subsequently, these substances have been identified as ingredients in numerous retail products (Auwärter *et al.*, 2009; Lindigkeit *et al.*, 2009; Hudson *et al.*, 2010; Nakajima et al., 2011; Uchiyama *et al.*, 2010a; Uchiyama *et al.*, 2010b; Uchiyama et al., 2010a,b, 2011; Microgram Bulletin, 2009; Dresen *et al.*, 2010; EMCCDA, 2009).

Synthetic cannabinoids trafficking was first reported in the United States in a December 2008 encounter, where a shipment of Spice was seized and analyzed by U.S. Customs and Border Patrol in Dayton, Ohio. Around the same time, in December 2008, JWH-018 and cannabicyclohexanol were identified by German forensic laboratories (EMCDDA, 2009). These substances may have existed and been abused some time prior to their identification (Psychonaut Web Mapping Research Group, 2009).

The popularity of these purported hallucinogenic substances and their associated products appears to have spread rapidly since January 2010 in several regions of the United States based on seizure exhibits and media reports. This trend appears to mirror those experienced in Europe since 2008 (EMCDDA, 2009). These substances are primarily found as ingredients in other products. These have also been abused alone as self-reported on internet discussion boards (Atwood *et al.*, 2010). Their abuse has been characterized with both acute and long term public health and safety issues.

As of January 13, 2012, forty-eight states in the U.S. as well as numerous local jurisdictions and countries have controlled at least one of the five synthetic cannabinoids of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol. Bans of the use of these synthetic cannabinoids by military personnel have also been issued in response to the abuse of synthetic cannabinoids and the related products (Bebarta *et al.*, 2010; communications to DEA).

Large seizures of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have occurred by law enforcement. NFLIS details over 5,450 reports from state and local forensic laboratories identifying JWH-018, JWH-073, JWH-200, CP-47,497 and/or cannabicyclohexanol in drug related exhibits for a period from January 2009 to December 2011 from 39 states.

Data gathered from published studies, supplemented by reports on Internet websites and personal communications indicate that these substances are often abused via smoking (Vandrey et al., 2012) for their psychoactive properties. Initial reports suggest the duration of effects in humans for JWH-018 to be 1-2 hours and CP-47,497 to be 5-6 hours (EMCDDA, 2009). The synthetic cannabinoids-laced products, such as Spice, "K2," and many others, are marketed as "legal" alternatives to marijuana. This characterization and their reputation as potent herbal intoxicants increased their popularity (Lindigkeit *et al.*, 2009). These substances alone or laced on plant material have the potential to be more harmful than cannabis due to their method of manufacture and the potency of the substances. These substances display higher potency *in vitro* and *in vivo* when compared to THC (Wiley *et al.*, 1998; Compton *et al.*, 1992; see Factor 2). Smoking mixtures of these substances abused for the purpose of achieving intoxication have resulted in numerous emergency room visits and calls to poison centers.

Youths appear to be the primary abusers, as supported by law enforcement encounters and reports from emergency rooms. However, all age groups have been discussed in media reports as abusing these substances and related products. Individuals, including minors, are purchasing these substances from Internet websites, gas stations, convenience stores, and head shops. There have also been reports of U.S. military personnel purchasing and abusing these synthetic cannabinoids (Johnson *et al.*, 2011), which has prompted bans of the use of these synthetic cannabinoids by military personnel (Bebarta *et al.*, 2010; communications to DEA). These substances, and products laced with these substances, are commonly marketed as "legal highs" and with the disclaimer "not for human consumption." As detailed in reports, law enforcement and public health officials are encountering the abuse of these substances.

Numerous herbal incense products have been found to contain one or more of these synthetic cannabinoids laced on plant material. There is no known explanation for the addition of these synthetic cannabinoids to plant material being marketed as herbal incense, other than for their psychoactive properties (Lindigkeit *et al.*, 2009). The psychoactive properties are directly linked to the synthetic cannabinoids laced on the plant material sold as retail products (Auwärter *et al.*, 2009; Atwood *et al.*, 2010, 2011; EMCDDA, 2009). To lace the plant material, the synthetic cannabinoid(s) is 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; observation from manufacturing laboratory encounters). No smell has been attributed to these products nor do these substances such as JWH-018 (marketed as Bonsai 18) have any role as a plant food. Two research articles propose that the packaging is professional and conspicuous and intended to target young people who are possibly eager to use cannabis, but who are afraid of the judicial consequences and/or association with illicit drugs (Lindigkeit *et al.*, 2009; Schifano *et al.*, 2009).

Dresen and colleagues (2011) found these substances are being abused by individuals in treatment with a positive rate of 63.3% in forensic psychiatric centers based on their sampling (Dresen *et al.*, 2011). U.S. Drug Courts have communicated concerns related to the abuse of synthetic cannabinoids and a response rate of greater than 30% by juveniles subject to routine drug screens from a sampling.

Summary

JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have been found alone and found laced on products that are marketed as herbal incense. The abuse of these substances and their associated products for their psychoactive effects has been widely reported and their popularity appears to have spread rapidly since January 2010. Prior to being temporarily placed in Schedule I on March 1, 2011, these products were promoted as legal alternatives to marijuana, were widely available over the Internet, and were found to be sold in gas stations, convenience stores, tobacco and head shops to all populations. As of January 13, 2012, forty-eight states in the U.S. as well as numerous local jurisdictions and countries have controlled at least one of the five synthetic cannabinoids.

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

HHS states that the current scope and duration of use of these five synthetic cannabinoids is likely underestimated because of the lack of widely available toxicological methods to identify its use using routine analyses (Peters and Martinez-Ramirez 2010).

Since these substances were never intended for human consumption, minimal information exists as to the health implications resulting from exposure to these substances (Griffiths *et al.*, 2010; Vardakou *et al.*, 2010). As forensic procedures and toxicology screens are being developed, the amount of information concerning these substances and the associated products is increasing. As a result, a better understanding regarding the abuse and harmful effects of these substances is being developed. The scientific literature and reports received by DEA suggest tolerance and dependence to synthetic cannabinoids may develop (Zimmerman *et al.*, 2009). Prior to the Final Order temporarily scheduling these substances, these products were sold over the Internet and found to be abused by diverse populations.

According to forensic laboratory data, the first documented encounter in the United States regarding synthetic cannabinoids laced on plant material occurred in conjunction with a U.S. Customs and Border Patrol analysis of Spice products entering the United States. However, these products are believed to have existed since 2004 (Psychonaut Web Mapping Research Group, 2009).

Large seizures of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have occurred by law enforcement. NFLIS details over 5,450 reports from state and local forensic laboratories identifying JWH-018, JWH-073, JWH-200, CP-47,497 and/or cannabicyclohexanol in drug related exhibits for a period from January 2009 to December 2011 from 39 States.

The abuse of synthetic cannabinoids has been associated with both acute and long-term public health and safety concerns. In the past year, increased exposure incidents have been documented by poison centers in the United States. The American Association of Poison Control Centers (AAPCC) has reported receiving 9,922 calls corresponding to products purportedly laced with these synthetic cannabinoids through December 31, 2011. Data from the U.S. 57 Poison Centers (PCs) indicate that they received 2,924 exposure calls in 2010 and 6,998 exposure calls

in 2011, relating to these synthetic cannabinoids.[5] A majority of exposure incidents resulted in seeking medical attention at health care facilities.

Exposure calls refer to actual or potential human exposure to a synthetic cannabinoid (e.g., inhalation, ingestion, topical exposure). The calls represented exposed individuals from all 50 states and the District of Columbia. There were a few calls regarding exposed individuals in Puerto Rico, U.S. Territories, foreign countries, and a category identified as "overseas/US military/diplomatic." Most of the synthetic cannabinoids reported by the poison centers were identified as "K2"/herbal blend (50.2%) and THC homologue (18.3%). In 25% of the cases, the product involved was unknown. Several exposures were determined to be JWH-018 (141), JWH-073 (12), HU-210 (6), JWH-015 (2), JWH-250 (2), and JWH-210 (1). A large majority of the exposures were due to intentional abuse, misuse, or suspected suicide (92.0%). The most common forms of the known synthetic cannabinoids were aerosol/mist/spray/gas, tablets/capsules/caplets, and powder/granules. Most of the exposures (86.0%) were described as acute.[6] Exposures described as acute-on-chronic[7] or chronic[8] accounted for approximately 4% and 3% of the cases, respectively. Males accounted for 74% of all exposures for 2010 and 2011. In every age group, predominantly males were exposed to the synthetic cannabinoids. Most of the exposed individuals were aged 18-25 years (42.4%) and under 18 (29.2%). A few of the callers (1.0%) identified the exposed individuals as being in their 20s. The most common route of administration for the synthetic cannabinoids is inhalation/nasal.

---

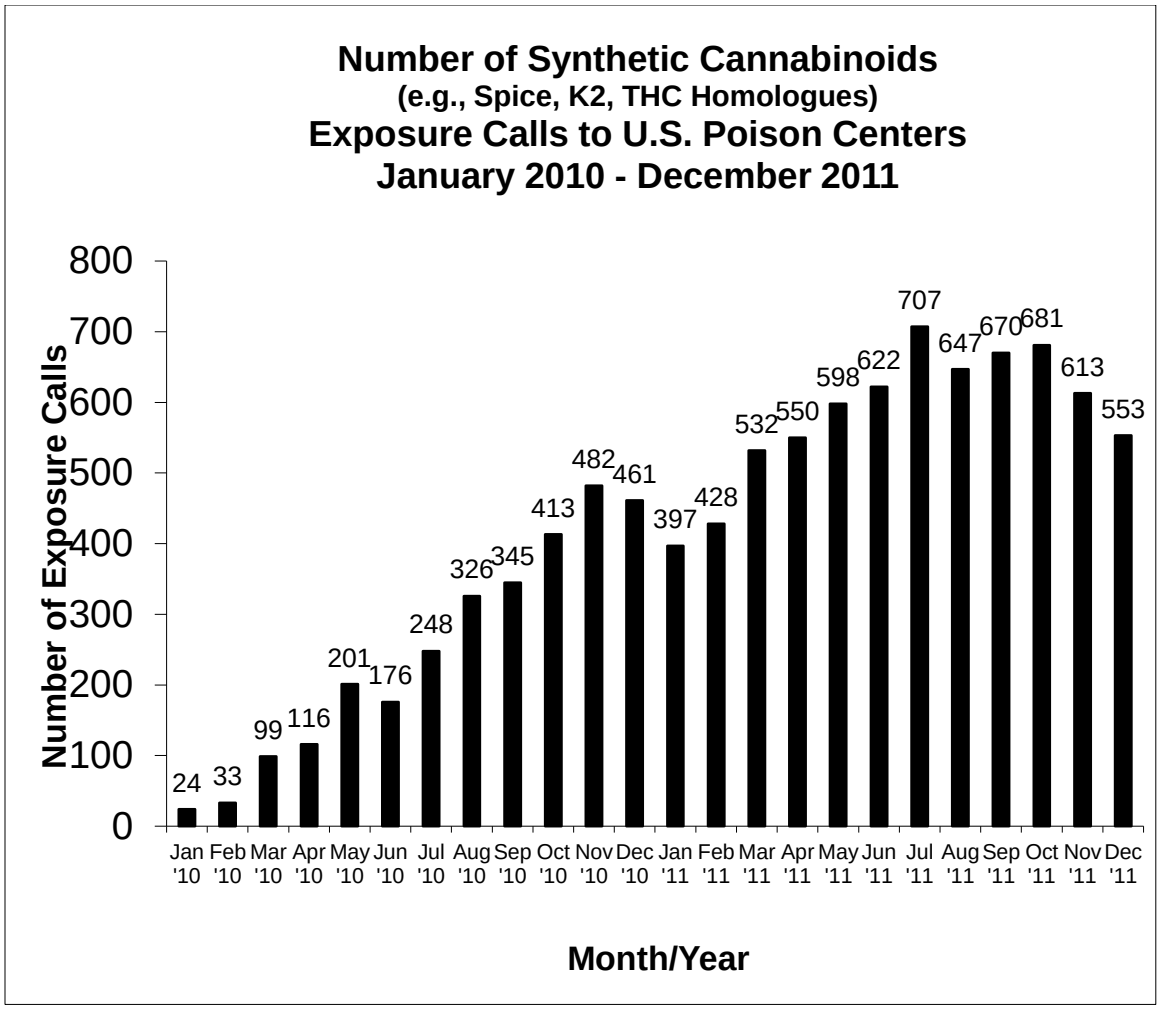
[5] The content of this report does not necessarily reflect the opinions or conclusions of the American Association of Poison Control Centers.

The American Association of Poison Control centers (AAPCC; http://www.aapcc.org) maintains the national database of information logged by the country's 57 Poison Centers (PCs). 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, or 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 PCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

[6] The AAPCC describes an acute chronicity as a single, repeated or continuous exposure occurring over a period of eight hours or less.

[7] Acute-on-chronic is a single exposure that was preceded by a continuous, repeated, or intermittent exposure occurring over a period exceeding eight hours.

[8] Chronic is a continuous, repeated, or intermittent exposure to the same substance lasting longer than eight hours.



Source: The American Association of Poison Control Centers (AAPCC) National Poison Data System.

DHHS states that case reports have demonstrated that herbal products containing synthetic cannabinoids produce physical dependence and a withdrawal syndrome (Zimmermann *et al.* 2009; Vardakou *et al.*, 2010). In one case report, the authors concluded that the patient satisfied criteria for a diagnosis of DSM-IV and ICD-10 dependency syndrome (Zimmermann *et al.* 2009). These signs of dependence and withdrawal are similar to that experienced with cannabis abuse (Zimmermann *et al.*, 2009, Müller *et al.*, 2010a; Vardakou *et al.*, 2010). Tolerance to these drugs may develop fairly rapidly with larger doses being required to achieve the desired effect (Zimmerman *et al.*, 2009; EMCDDA, 2009). Psychosis is also attributed to the abuse of these substances (Every-Palmer, 2010, 2011; Müller *et al.*, 2010a; Law enforcement reports to DEA).

The popularity and use of these substances was identified as a major problem in Europe in 2008 (EMCDDA, 2009). It is believed that Internet advertising has contributed to the popularity of these substances and deep concerns exist regarding the limited knowledge of the manufacturers of these substances (Schifano *et al.*, 2009).

The increased abuse of these synthetic cannabinoids in the United States is supported by an increasing number of encounters by law enforcement. Over the past year, in the United States, there has been a significant increase in availability, trafficking, and abuse of these substances as evident from the increasing number of encounters reported by forensic laboratories (NFLIS and STRIDE data). The initial indication of the evidence of abuse of both JWH-018 and cannabicyclohexanol appeared in 2009 upon identification in products. Since then, other synthetic cannabinoids including JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol were encountered and others are emerging in response to enacted state legislation (JWH-081, JWH-250, JWH-398, JWH-210, JWH-122, JWH-251, JWH-019, JWH-203, RCS-8, RCS-4, AM2201, and AM 694). This represents a transition to new synthetic cannabinoids in order to circumvent legal controls, where product manufacturing and synthesis laboratories have been discovered, and laboratories have been found manufacturing products by lacing plant material with synthetic cannabinoids.

The amount of information regarding these substances and related products appears to be rapidly increasing in the scientific literature. Hudson and colleagues (2010) analyzed 16 different Spice products and multiple products marketed under the same name for a total of 40 analyses. The products contained previously identified synthetic cannabinoids along with new structurally related substances. Each product analyzed and marketed in this Spice class of products contained multiple synthetic cannabinoids. In the majority of exhibits, JWH-018 and cannabicyclohexanol were found together on the same material, and in a few instances one or the other was the sole synthetic cannabinoid identified. To a lesser extent, other synthetic cannabinoids such as JWH-073, JWH-081, JWH-398, and CP-47,497 were also found in these products. The investigators stated that variants of products were anticipated to differ in ingredients and these ingredients varied in relative amounts from batch to batch. Furthermore, the authors proposed that ingredient variability might account for the differential effects anecdotally reported by the users of these products.

Other product analyses have yielded very important information regarding these synthetic substances. Dresen and colleagues (2010) analyzed 140 samples from 68 different products during the period of June 2008 to September 2009. The investigators found the composition of the products changed over time and neither the seller nor consumer could predict the composition of these products. Products were found to contain cannabicyclohexanol and JWH-018, and new synthetic cannabinoids JWH-073, JWH-250, and JWH-398 were also identified. In another study by Lindigkeit and colleagues (2009), 11 herbal incense products were analyzed from the German market. Products were found to vary in amount of synthetic cannabinoid laced on the plant material, ranging from 2.3 mg/g to 22.9 mg/g. Prior to their ban in Germany, all products analyzed contained cannabicyclohexanol or JWH-018. After their ban, new synthetic cannabinoids were found in second generation products. The analysis of numerous products from the Japanese market by Uchiyama *et al.* (2010a) found JWH-018 and cannabicyclohexanol being observed as ingredients, with JWH-073 and CP-47,497 detected in the analyzed products to a lesser extent. A total of 46 different herbal products were analyzed and 44 were found to contain synthetic cannabinoids.

Summary

The abuse of synthetic cannabinoids, characterized by reported adverse health effects, is documented in the scientific literature and by law enforcement encounters. Numerous calls have been received by poison centers regarding the abuse of products potentially laced with synthetic cannabinoids as well as presentation at emergency departments. Some of the adverse health effects reported in response to the abuse of these substances include vomiting, anxiety, agitation, irritability, seizures, hallucinations, tachycardia, elevated blood pressure, and loss of consciousness.

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

Law enforcement, military, and public health officials have reported exposure incidents that demonstrate the dangers associated with these substances to both the individual abusers and other affected individuals. As reiterated by Dowling and Regan (2011), these substances were never intended for human use. Two suicides, one also involving a homicide, have been linked to the abuse of synthetic cannabinoids (law enforcement communication to DEA). Warnings regarding the dangers of synthetic cannabinoid abuse and associated products have been issued by numerous state public health departments and poison centers and private organizations. Detailed product analyses describe variations in the amount and type of synthetic cannabinoid laced on the plant material; this is true even within samplings of the same product (Hudson *et al.*, 2010). Wells and Ott (2011) stated concern regarding the possibility of the occurrence of a serotonin syndrome related to synthetic cannabinoids of the indole structural class, and this concern was in part due to the similarity to serotonin. Additionally, it has been suggested that extreme variability in composition and potency place abusers of these products at risk of serious, if not lethal, outcomes (Fattore and Fratta, 2011).

HHS states that JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol share the pharmacological effects of THC, and that substances with cannabinoid agonist activity present similar risks to the public health as JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol. Because they share pharmacological similarities with the Schedule I substance THC, the synthetic cannabinoids JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol pose risks to the abuser (Compton *et al.*, 1992; Weissman *et al.*, 1992; Wiley *et al.*, 1998). According to HHS, *in silico* analyses predicted the adverse health effects of these synthetic cannabinoids on cardiovascular, reproductive and genetic systems. The chronic abuse of products laced with synthetic cannabinoids has been linked to addiction and withdrawal (Vardakou *et al.*, 2010). Two separate controlled investigations involving a total of four subjects were undertaken to evaluate the effects of two products. Both products were found to be laced with JW-018 and one of the products also contained cannabicyclohexanol. Two researchers described potent effects upon smoking the product "Spice Diamond." Ten minutes post-exposure the subjects experienced noticeable effects in the form of reddened conjunctivae, significant increases in pulse rates, xerostomia (dry mouth), and an alteration of mood and perception (Auwärter *et al.*, 2009). Another report described sickness, sedation, and xerostomia which were accompanied by hot flashes and burning eyes, all of which immediately followed the smoking of the product "Smoke." (Teske *et al.*, 2010). This issue is further complicated by the finding that similar products have been found to vary in the synthetic cannabinoid and amount

laced on the plant material. Dependence, withdrawal, and psychotic episodes have also been associated with products purported to contain these synthetic cannabinoids (Zimmermann *et al.*, 2009; Müller *et al.*, 2010a). Numerous emergency department admissions have been connected to these substances and emergency room physicians have described morbidity associated with these substances and products (reported by law enforcement; Vearrier and Osterhoudt, 2010; Schneir *et al.*, 2011; communications to DEA from public health officials). Additionally, violent episodes are linked to smoking these substances (multiple law enforcement communications). Health warnings have been issued by numerous state public health departments and poison centers describing adverse health effects associated with smoking (inhaling) these products including, agitation, vomiting, tachycardia, elevated blood pressure, seizures, hallucinations and non-responsiveness. These findings are further supported by the occurrence of paranoia and hallucinations described by some patients (Banerji *et al.*, 2010; Bebarta *et al.*, 2010).

Numerous individuals have presented at emergency departments in response to exposure to products containing synthetic cannabinoids. In one case reported by Schneir and colleagues (2011), two females (20 and 22 years of age) presented at the ED in response to smoking an herbal incense product. Both individuals reported daily smoking of various Spice products. The case reports listed adverse health effects which were consistent with those associated with these substances and associated products, such as, anxiety, tremors, psychosis, and elevated pulse. Laboratory analysis of the herbal incense product found JWH-018 and JWH-073 to be present. The urine drug screen for one of patients was negative for other drugs of abuse.

Vearrier and Osterhandt (2010) reported the emergency room admission of a 17-year old female in response to smoking JWH-018. Approximately fifteen minutes after a single "bong hit" from a water pipe, she presented at the emergency department with tachycardia (mildly elevated), agitation, muscle fasciculations, and hypokalemia. A urine immunoassay for drugs of abuse tested positive for tetrahydrocannabinol. Two of her friends were also taken to the hospital in response to trying a "new marijuana" for the first time.

Canning and colleagues (2010) described the presentation of an 18-year old after smoking an herbal incense product with acute intoxication complicated by severe gastrointestinal distress. The previously healthy individual presented thirty minutes after smoking the product "K2 Summit" with tremors, blurred peripheral vision, nausea, and persistent vomiting with retching. The patient was described by his friends as "having difficulty walking" and "mumbling." Liquid chromatography–mass spectrometry/mass spectrometry (LCMS/MS) analysis of a serum sample obtained from the patient 4.5 h post exposure identified JWH-018 at concentration of 0.5 ng/mL. A drug screen was negative for other drugs of abuse.

Müller and colleagues (2010b) describe the rapid onset of a panic attack in a 21-year old male with attention deficient hyperactivity disorder after a third-ever consumption of Spice. The patient developed blurred vision and unsteady gait and reported profuse sweating, severe weakness, and massive heart palpitations. Additionally, the patient experienced acute onset of an agonal state with the fear of being perceived as ignorant by friends. The panic attack was followed by a vegetative hyperirritability that lasted for more than two hours.

Kamat and colleagues (2012) described the presentation of an 18-year-old man who smoked a product alleged to contain synthetic cannabinoids and one hour later developed a severe global headache. Imaging revealed an intracranial hemorrhage determined to be caused by a small artery aneurysm. No toxicological or forensic analysis was performed to confirm the presence of synthetic cannabinoids in the product smoked or in the patient's blood.

Self-reports on internet discussion boards describe abuse of these substances alone as well as abuse of these substances as product ingredients. The effects of these substances are described as being highly potent and cannabis-like. JWH-018 has been described as both a potent and efficacious CB1 receptor agonist. This likely explains the ability of this substance and its herbal products to produce cannabis-like effects (Atwood *et al.*, 2010). The duration of effects in humans compared to cannabis seems to be shorter for JWH-018 (1-2 hours) and longer for cannabicyclohexanol (5-6 hours) (Auwärter *et al.*, 2009). The most common route of administration of these substances and associated products is by smoking, either by using a standard pipe or a water pipe, or by rolling the plant material in cigarette papers.

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). As mentioned above, there are reported instances of emergency department admissions in association with the abuse of these synthetic cannabinoids.

Convulsive effects

A recent case report by Schneir and Baumhaeher (2011) describes a 19-year-old male patient who had two witnessed generalized convulsions soon after smoking a Spice product that was later confirmed to contain JWH- 018 and three other different synthetic cannabinoids (JWH-081, JWH-250, and AM-2201). Convulsions have also been described in another published report for which there was no laboratory confirmation for the presence of synthetic cannabinoids in the products involved (Simmons *et al.*, 2011a). In yet another report, in which there was laboratory confirmation for metabolites of the synthetic cannabinoid JWH-018, a patient was interpreted by the authors as having had a possible convulsion (Simmons *et al.*, 2011b).

Convulsions associated with recreational use of Cannabis sativa (marijuana) use appear to be rare (Ng *et al.*, 1990; Gordon and Devinsky, 2001), and have been reported after accidental ingestion in children (Bonkowsly *et al.*, 2005; Spadari *et al.*, 2009). Shneir and colleagues discuss the hypothesis that the absence of the anticonvulsant cannabidiol (Consroe *et al.*, 1981) in the synthetic cannabinoids-containing products might contribute to the frequency and mechanism of convulsions associated with these products.

Automotive accidents

Abusers have been suspected of driving under the influence of these substances. In one incident where an automobile was driven through a residence, the individual claimed to have no memory of the event. A laboratory analysis of the product and pipe from the incident encounter found JWH-018 and the urine analysis identified JWH-018 metabolites. A hospital drug analysis in response to this event found no other drugs of abuse based on the hospital drug screen.

Psychosis

Large scale epidemiological studies indicate that marijuana may increase risk of psychosis in vulnerable populations, i.e., individuals predisposed to develop psychosis (Andreasson *et al.*, 1987) and exacerbate psychotic symptoms in individuals with schizophrenia (Schiffman *et al.*, 2005; Hall *et al.*, 2004; Mathers and Ghodse, 1992; Thornicroft, 1990; 76 FR 40552-89).

Recent reports suggest that synthetic cannabinoid-receptor agonists-containing products may also precipitate psychosis in vulnerable individuals (Every-Palmer *et al.*, 2010, 2011). Some of those reports do not have definite forensic identification of the cannabinoid substances present in the products, such as Spice, "K2," or "Aroma."

Semi-structured interviews were used to examine the use and effects of JWH-018 purported to be the main active ingredient of the product "Aroma" by 15 patients with serious mental illness in a New Zealand forensic and rehabilitative service (Every-Palmer *et al.*, 2011). All 15 subjects were familiar with a locally available JWH-018 containing product called "Aroma" and 86% reported having used it. They credited the product's potent psychoactivity, legality, ready availability and non-detection in drug testing as reasons for its popularity, with most reporting it had replaced cannabis as their drug of choice. Anxiety and psychotic symptoms were common after use, with 69% of users experiencing or exhibiting symptoms consistent with psychotic relapse after smoking JWH-018. This manifested as the sudden re-emergence of florid psychosis: predominantly agitation, disorganization and delusional beliefs (paranoid and grandiose types) in previously stable patients with histories of mental illness (Every-Palmer, 2010).

A case report presents the synthetic cannabinoid-containing product Spice as a trigger for an acute reactivation of cannabis induced recurrent psychotic episodes (Muller *et al.*, 2010). The authors discuss the case of a twenty-five year old male who had a history of cannabis-induced recurrent psychotic episodes but had been stable with only minor symptoms over the previous two years. Immediately after Spice abuse, cannabis-induced recurrent psychotic symptoms were reactivated, but in addition the patient experienced further psychotic symptoms not previously displayed.

Fatalities

A fatality confirmed to be related to the abuse of JWH-018 was reported in 2011. A 19-year old sophomore in South Carolina died four days after collapsing on a campus basketball court. Toxicological analysis revealed ingestion of JWH-018. The coroner ruled the cause of death drug toxicity and organ failure.

Other fatalities have been reported to be linked to the abuse of synthetic cannabinoid-containing products, but toxicology confirmation has generally lacked, and thus the exact substances involved were not determined.

Summary

The abuse of these substances presents the potential for accidental overdose with a risk of complications.

Factor 7: Its Psychic or Physiological Dependence Liability

HHS states that the pharmacological profile of JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol strongly suggests that they possess a physiological and psychological dependence liability that is similar to that of marijuana and related cannabinoids, such as THC. Thus, they would have a high psychic and physiologic dependence capacity.

Physical dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001). No laboratory controlled clinical studies of the psychic or physical dependence potential of these five cannabinoids are currently available.

In an internet-based survey study conducted with adults reporting at least one lifetime use of a Spice product, a series of questions were included to evaluate participants' possible dependence on these synthetic cannabinoids (Vandrey *et al.*, 2012). It was found that a subset of respondents met DSM-IV (American Psychiatric Association, 2000) criteria for abuse (37%) and dependence (12%). Using Spice in a hazardous situation was the most commonly endorsed abuse criteria (27%), and being unable to cut down or stop Spice use (38%), experiencing symptoms of tolerance (36%), using for longer periods than originally intended (22%) and having interference with other activities (18%) were the most commonly reported dependence criteria. Despite endorsing problems related to Spice use, no respondent had ever sought or received treatment. Withdrawal symptoms following cessation of Spice use were rare, and most prevalent among more frequent users. The most commonly reported withdrawal effects were headaches (15%), anxiety/nervousness (15%), coughing (15%), insomnia/sleep disturbance (14%), anger/irritability (13%), impatience (11%), difficulty concentrating (9%), restlessness (9%), nausea (7%), and depression (6%). These effects are, overall, similar to those reported during withdrawal from marijuana (Budney *et al.*, 1999).

Case reports have shown that herbal products containing synthetic cannabinoids could produce physical dependence and a withdrawal syndrome. The HHS analysis discusses one case report in which the authors concluded that the patient satisfied criteria for a diagnosis of DSM-IV and ICD-10 dependency syndrome (Zimmermann *et al.* 2009). In the report, a 20-year old German patient had smoked "Spice Gold" daily for an 8-month period. Samples of "Spice Gold" have been verified to contain JWH-018. During this time, he increased his dose from 1g to approximately 3g/day, indicating the possible development of tolerance. The patient reported a desire to continue use of the product despite cognitive impairment. His use of "Spice Gold" led him to neglect professional obligations, and he was voluntarily admitted to the hospital. During his admittance, the patient experienced elevated blood pressure, restlessness, drug craving, nightmares, sweating, nausea, tremor and headache. The patient was still described as "irritable" on day 10. The time course for the resolution of symptoms was not detailed (Zimmermann *et al.*, 2009).

Because these substances act through the same molecular target as THC, the main active ingredient of marijuana, it can be reasonably expected that their physical dependence liability

will be similar. Long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation as well as psychic addiction or dependence. The marijuana withdrawal syndrome consists of symptoms such as restlessness, irritability, mild agitation, insomnia, EEG disturbances, nausea, cramping and decrease in mood and appetite that may resolve after four days, and may require in-hospital treatment (Haney *et al.*, 1999). It is distinct and mild compared to the withdrawal syndromes associated with alcohol and heroin use (Budney *et al.*, 1999; Haney *et al.*, 1999).

Budney *et al.* (1999) examined the withdrawal symptomatology in 54 chronic marijuana abusers seeking treatment for their dependence. The majority of the subjects (85 percent) reported that they had experienced symptoms of at least moderate severity. Fifty-seven percent (57 percent) reported having six or more symptoms of at least moderate severity while 47 percent experienced four or more symptoms rated as severe. The most reported mood symptoms associated with the withdrawal were irritability, nervousness, depression, and anger. Some of the other behavioral characteristics of the marijuana withdrawal syndrome were craving, restlessness, sleep disruptions, strange dreams, changes in appetite, and violent outbursts.

Factor 8: Whether the substance is an immediate precursor of a substance already controlled

JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol are not considered immediate precursors of any controlled substance of the CSA as defined by Title 21, U.S.C § 802(23).

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 HHS, DEA finds that JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol meet the following criteria for placement in Schedule I of the CSA pursuant to 21 U.S.C. 812 (b)(1):

1. JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have a high potential for abuse.

Each of the five substances considered in this review is a synthetic substance that produces cannabinoid-like effects. HHS states that the pharmacological similarity of JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol to THC makes it reasonable to assume that their potential for abuse is high and would be similar to that of marijuana and THC, both of which are cannabinoids and are controlled in Schedule I of the CSA. According to the results of the 2011 Monitoring the Future survey of high schools students, 1 in 9 high school seniors (11.4%) have used "synthetic marijuana" in the past year (Johnston et al., 2012). It is one of the most frequently mentioned among high school seniors in the survey, second only to marijuana.

2. JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have no currently accepted medical use in treatment in the United States.

HHS states that there are no approved NDAs for JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol in the United States. There is no known therapeutic application for JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol. Therefore, JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol have no currently accepted medical use in the United States.

3. There is a lack of accepted safety for use of JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol under medical supervision.

HHS states that, the safety for use under medical supervision of JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol is not determined. In addition, case reports have shown a number of adverse consequences thought to be related to abuse of JWH-018, JWH-073, and synthetic cannabinoids related to JWH-200, CP-47,497, and cannabicyclohexanol. Thus, there is a lack of accepted safety for use of these substances under medical supervision.

References

Atwood BK, Huffman J, Striker A, and Mackie K (2010). **JWH018, a common constituent of 'Spice' herbal blends, is a potent and efficacious cannabinoid CB1 receptor agonist.** *British Journal of Pharmacology* 160(3): 585-593.

Atwood BK, Lee D, Straiker A, Widlanski TS, Mackie K (2011). **CP47,497-C8 and JWH073, commonly found in 'Spice' herbal blends, are potent and efficacious CB(1) cannabinoid receptor agonists.** European Journal of Pharmacology 659(2-3):139-45.

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.

Auwärter V, Dresen S, Weinmann W, Müller M, Pütz M, and Ferreirós N (2009). **Spice and other herbal blends: harmless incense or cannabinoid designer drugs?** *Journal of Mass Spectrometry* 44(5):832-837.

Balster RL and Prescott WR (1992). **Δ9-Tetrahydrocannabinol discrimination in rats as a model for cannabis intoxication.** *Neuroscience and Biobehavioral Reviews* 16:55-62.

Bell MR, D'Ambra TE, Kumar V, Eissenstat MA, Herrmann JL, Wetzel JR, Rosi D, Philion RE, Daum SJ, Hlasta DJ, Kulling RK, Ackerman JH, Haubrich DR, Luttinger DA, Baizman ER, Miller MS, and Ward SJ (1991). **Antinociceptive (aminoalkyl)indoles.** *Journal of Medicinal Chemistry* 34(3):1099-1110.

Bebarta VS, Varney S, Sessions D, Barry D, and Borys D (2010). **Spice: A New "Legal" Herbal Mixture Abused by Young Active Duty Military Personnel. NACCT 2010 Abstracts [abstract].** *Clinical Toxicology* 48(6): 604-667.

Banerji S, Deutsch CM, and Bronstein AC (20010). **Spice Ain't So Nice. NACCT 2010 Abstracts [abstract].** *Clinical Toxicology* 48(6): 604-667.

Benford DM and Caplan JP. (2011). **Psychiatric sequelae of spice, K2, and synthetic receptor agonists.** *Psychosomatics* 52(3):295.

Brents LK, Reichard EE, Zimmerman SM, Moran JH, Fantegrossi WE, and Prather PL (2011). Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH-018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. *PLOS One* 6(7):e21917

Budney AJ, Novy PL, Hughes JR (1999). **Marijuana withdrawal among adults seeking treatment for marijuana dependence.** *Addiction* 94(9):1311-22.

Camp NE (2011). **Synthetic Cannabinoids.** *Journal of Emergency Nursing* 37(3):292-3.

Canning JC, Ruha A-M, Pierce R, Torrey M, and Reinhart SJ (2010). **Severe GI distress after smoking JWH-018. NACCT 2010 Abstracts [abstract].** *Clinical Toxicology* 48(6): 604-667.

Chimalakonda KC, Moran CL, Kennedy PD, Endres GW, Uzieblo A, Dobrowolski PJ, Fifer, EK, Lapoint J, Nelson LS, Hoffman RS, James LP, Radominska-Pandya A, and Moran JH (2011). **Solid-phase extraction and quantitative measurement of omega and omega-1 metabolites of JWH-018 and JWH-073 in human urine.** *Analytical Chemistry* 83(16):6381-6388.

Compton DR, Gold LH, Ward SJ, Balster RL, and Martin BR (1992a). **Aminoalkylindole analogs: cannabimimetic activity of a class of compounds structurally distinct from Δ^9-Tetrahydrocannabinol.** *Journal of Pharmacology and Experimental Therapeutics* 263(3): 1118-1126.

Compton DR, Johnson MR, Melvin LS, and Martin BR (1992b). **Pharmacological profile of a series of bicyclic cannabinoid analogs: classification as cannabimimetic agents.** *Journal of Pharmacology and Experimental Therapeutics* 260(1): 201-209.

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

Department of Health and Human Services (2012a). **Basis for the Recommendation to Place 1-Pentyl-3-(1-Naphthoyl)Indole (JWH-018) and its Salts in Schedule I Of The Controlled Substances Act (CSA)**.

Department of Health and Human Services (2012b). **Basis for the Recommendation to Place [1-[2-(4-Morpholinyl)Ethyl-1H-Indol-3yl]-1-Naphthalenyl-Methanone (JWH-200) and its Salts in Schedule I Of The Controlled Substances Act (CSA).**

Department of Health and Human Services (2012c**). Basis for the Recommendation to Place Naphthalenyl-1-yl-(1-Butylindole-3-yl)-Methanone (JWH-073) and its Salts in Schedule I Of The Controlled Substances Act (CSA).**

Department of Health and Human Services (2012d**).** Basis for the Recommendation to Place 5-(1,1- Dimethylheptyl)-2-[(1R,3S)-3-Hydroxycyclohexyl Phenol] and its Enantiomer 5-(1,1-Dimethylheptyl)-2-[(1S,3R)-3-Hydroxycyclohexyl Phenol](CP 47,497), and **their Salts** in Schedule I of the Controlled Substances Act (CSA),

Department of Health and Human Services (2012e**).** Basis for the Recommendation to Place Cannabicyclohexanol, (C8)-CP 47,497, Also Known as 5-(1,1- Dimethyloctyl)-2-[(1R,3S)-3-Hydroxycyclohexyl Phenol] and its Enantiomer 5-(1,1- Dimethyloctyl)-2-[(1S,3R)-3-Hydroxycyclohexyl Phenol], and **its Salts** in Schedule I of the Controlled Substances Act (CSA),

Dowling G and Regan L (2011). **A method for CP 47,497 a synthetic non-traditional cannabinoid in human urine using liquid chromatography tandem mass spectrometry.** *Journal of Chromatography B* 879:253-259.

Dresen S, Ferreiros N, Putz M, Westphal F, Zimmermann R, and Auwarter V (2010). **Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds.** *Journal of Mass Spectrometry* 45(10): 1186-1194.

Dresen S, Kneisel S, Weinmann W, Zimmermann R, and Auwärter V (2011). **Development and validation of a liquid chromatography-tandem mass spectrometry method for the quantitation of synthetic cannabinoids of the aminoalkylindole type and methanandamide in serum and its application to forensic samples.** *Journal of Mass Spectrometry* 46(2):163-171.

Eissenstat MA, Bell MR, D'Ambra TE, Alexander EJ, Daum SJ, Ackerman JH, Gruett MD, Kumar V, Estep KG, Olefirowicz EM, Wetzel JR, Alexander MD, Weaver JD, Haycock DA, Luttinger DA, Cassiano FM, Chippart SM, Kuster JE, Stevenson JI, and Ward SJ (1995). **Aminoalkylindoles: Structure-Activity Relationships of Novel Cannabinoid Mimetics.** *Journal of Medicinal Chemistry* 38: 3094-3105.

EMCDDA (2009). Action on new drugs briefing paper: **Understanding the 'Spice' Phenomenon.** EMCDDA expert meeting, March 6, 2009, Lisbon.

Ernst L, Schiebel H-M, Theuring C, Lindigkeit R, and Beuerle T (2011). **Identification and characterization of JWH-122 used as new ingredient in "Spice-like" herbal incenses.** *Forensic Science International* 208:e31-e35.

Every-Palmer S (2010). **Warning: legal synthetic cannabinoid-receptor agonists such as JWH-018 may precipitate psychosis in vulnerable individuals.** *Addiction* 105:1859-1860.

Every-Palmer S (2011). **Synthetic cannabinoid JWH-018 and psychosis: an explorative study.** *Drug and Alcohol Dependence* 117(2-3):152-7.

Fattore L, Fratta W (2011). **Beyond THC: The New Generation of Cannabinoid Designer Drugs**. *Frontiers in Behavioral Neuroscience* 5:60. Epub Sep 21.

Gerard CM, Mollereau C, Vassart G, and Parmentier M (1991). **Molecular cloning of a human cannabinoid receptor which is also expressed in testis.** *Biochemical Journal* 279(pt 1):129-134.

Ginsburg BC, Schulze DR, Hruba L, and McMahon LR (2012). **JWH-018 and JWH-073: Δ^9-tetrahydrocannabinol-like discriminative stimulus effects in monkeys**. *Journal of Pharmacology and Experimental Therapeutics* 340(1):37-45.

Griffin G, Atkinson PJ, Showalter VM, Martin BR, and Abood MW (1998). **Evaluation of cannabinoid receptor agonists and antagonists using the guanosine-5'-O-(3-[^{35}S]thio)-triphosphate binding assay in rat cerebellar membranes.** *The Journal of Pharmacology and Experimental Therapeutics* 285:553-560.

Griffiths P, Sedefov R, Gallegos A, and 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.

Grigoryev A, Savchuk S, Melnik A, Moskaleva N, Dzhurko J, Ershov M, Nosyrev A, Vedenin A, Izotov B, Zabirov I, and Rozhanets V (2011). **Chromatography-mass spectrometry studies on the metabolism of synthetic cannabinoids JWH-018 and JWH-073, psychoactive components of smoking mixtures.** *Journal of Chromatography B* 879 (15-16):1126-36.

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW (1999). **Abstinence symptoms following smoked marijuana in humans**. *Psychopharmacology (Berl)* 141(4):395-404.

Hanus L, Breuer A, Tchilibon A, Shiloah S, Goldenberg D, Horowitz M, Pertwee RG, Ross AA, Mechoulam R, and Fride E (1999). **HU-308: a specific agonist for CB(2), a peripheral cannabinoid receptor.** *Proceedings of National Academy of Sciences USA* 96:14228-14233.

Hermanns-Clausen M, Sauer O, Gerber G, Faerber E, Koch IE, Hentschel H, Seidel C, Stedtler U, and Auwärter (2009). **"New Herbal Drugs" of Abuse: Spice and Smoke. Abstracts of the 2009 International Congress of the European Association of Poison Centres and Clinical Toxicologists, 12-15 May 2009, Stockholm, Sweden [abstract].** *Clinical Toxicology* 47(5): 436-510.

Hudson S and Ramsey J (2011). **The emergence and analysis of synthetic cannabinoids.** *Drug Testing and Analysis* 3:466-78.

Hudson S, Ramsey J, King L, Timbers S, Maynard S, Dargan PI, and 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 (2009). **Cannabimimetic indoles, Pyrroles, and indenes: Structure-activity relationships and receptor interactions.** *Cannabinoid Receptors*, Reggio PH, Ed, Chapter 3, 49-98, Humana, New York

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

Huffman JW, Mabon R, Wu M-J, Lu J, Hart R, Hurst DP, Reggio PH, Wiley JL, and Martin BR (2003). **3-Indolyl-1-naphthylmethanes: New cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB1 cannabinoid receptor.** *Bioorganic & Medicinal Chemistry* 11:539-549.

Hutter M, Broecker S, Kneisel S, and Auwärter V (2012). **Identification of the major urinary metabolites in man of seven synthetic cannabinoids of the aminoalkylindole type present as adulterants in 'herbal mixtures' using LC-MS/MS techniques.** *Journal of Mass Spectometry* 47(1):54-66.

Järbe TUC, Li C, Vadivel SK, and Makriyannis A (2010). **Discriminative stimulus functions of methanandamide and Δ^9-THC in rats: tests with aminoalkylindoles (WIN55,212-2 and AM678) and ethanol.** *Psychopharmacology* 208(1):87-98.

Järbe TU, Deng H, Vadivel SK, Makriyannis A (2011). **Cannabinergic aminoalkylindoles, including AM678=JWH018 found in 'Spice', examined using drug (Δ(9)-tetrahydrocannabinol) discrimination for rats**. *Behavioral Pharmacology* 22(5-6):498-507.

Johnson LA, Johnson RL, and Alfonzo (2011). **Spice: A legal marijuana equivalent.** *Military Medicine* 176(6):718.

Johnston LD, O'Malley PM, Bachman JG, and Schulenberg JE (2012). **Monitoring the Future national results on adolescent drug use: Overview of key findings, 2011**. Ann Arbor: Institute for Social Research, The University of Michigan.

Kamat AS, Aliashkevich AF, Denton JR, and Fitzjohn TP (2012). **Case report: Headache after substance abuse: A diagnostic dilemma.** *Journal of Clinical Neuroscience.* Epub January 13, 2012

Lapoint J, James LP, Moran CL, Nelson LS, Hoffman RS, Moran JH (2011**). Severe toxicity following synthetic cannabinoid ingestion**. *Clinical Toxicology* 49(8):760-4.

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

Mackie K. (2005). **Distribution of cannabinoid receptors in the central and peripheral nervous system.** *Handbook of Experimental Pharmacology* 168:299-325.

Martin BR, Compton DR, Thomas BF, Prescott WR, Little PJ, Razdan RK, Johnson MR, Melvin LS, Mechoulam R, and Ward SJ (1991). **Behavioral, biochemical, and molecular modeling evaluations of cannabinoid analogs.** *Pharmacology Biochemistry and Behavior* 40:471-478.

Matsuda IA, Lolait SJ, Brownstein MJ, Young AC, and Bonner TI (1990). **Structure of a cannabinoid receptor and functional expression of the cloned cDNA.** *Nature* 346:561-564.

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

Melvin LS, Milne GM, Johnson MR, Subramaniam B, Wilken GH, and Howlett AC (1992). **Structure-activity relationships for cannabinoid receptor-binding and analgesic activity: studies of bicyclic cannabinoid analogs.** *Molecular Pharmacology* 44:1008-1015.

Microgram Bulletin (2009). **Intelligence alert - "Spice" - Plant material(s) laced with synthetic cannabinoids or cannabinoid mimicking compounds.** *Microgram Bulletin* March 2009 42 (3): 23-24.

Möller I, Wintermeyer A, Bender K, Jübner M, Thomas A, Krug O, Schänzer W, and Thevis M (2011). **Screening for the synthetic cannabinoid JWH-018 and its major metabolites in human doping control.** *Drug Testing and Analysis* 3:609-20.

Moran CL, Le V-H, Chimalakonda KC, Smedley AL, Lackey FD, Owen SN, Kennedy PD, Endres GW, Ciske FL, Kramer JB, Kornilov AM, Bratton LD, Dobrowolski PJ, Wessinger WD, Fantegrossi WE, Prather PL, James LP, Radominska-Pandya A, Moran JH (2011). **Quantitative measurement of JWH-018 and JW-073 metabolites excreted in human urine.** *Analytical Chemistry* 83(11):4228-4236.

Müller H, Sperling W, Köhrmann M, Huttner HB, Kornhuber J, and Maler J- M (2010a). **The synthetic cannabinoid Spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes.** *Schizophrenia Research* 118(1-3):309-310.

Müller H, Huttner HB, Köhrmann M, Wielopolski JE, Kornhuber J, and Sperling W (2010b). **Panic attack after Spice abuse in patient with ADHD.** *Pharmacopsychiatry* 43:152-154.

Nakajima J, Takahashi M, Seto T, Kanai C, Suzuki J, Yoshida M, and Hamano T (2011). **Identification and quantitation of two benzoylindoles AM-694 and (4-methoxyphenyl)(1-pentyl-1H-indol-3-yl)methanone, and three cannabinomimetic naphthylindoles JWH-210, JWH-122, and JWH-019 as adulterants in illegal products obtained via the Internet.** *Forensic Toxicology* 29:95-110.

National Institute of Drug Abuse (NIDA) (2011a). 1-pentyl-3-(1-naphthoyl)indole (JWH-018). Test of Substitution for the Discriminative Stimulus Effects of Delta(9)-THC. June 30, 2011.

National Institute of Drug Abuse (NIDA) (2011b). 1-[2-(4-Morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200). Test of Substitution for the Discriminative Stimulus Effects of Delta(9)-THC. October 8, 2011.

National Institute of Drug Abuse (NIDA) (2012a) 1-Butyl-3-(1-naphthoyl)indole (JWH-073). Test of Substitution for the Discriminative Stimulus Effects of Delta(9)-THC. January 17, 2012.

National Institute of Drug Abuse (NIDA) (2012b) CP-47,497 C8 homolog (cannabicyclohexanol). Test of Substitution for the Discriminative Stimulus Effects of Delta(9)-THC. January 26, 2012.

Pacheco M, Childers SR, Arnold R, Casiano F, and Ward SJ (1991). **Aminoalkylindoles: actions on specific G-protein-linked receptors.** *Journal of Pharmacology and Experimental Therapeutics* 257(1):170-183.

Piomelli D (2005. **The endocannabinoid system: a drug discovery perspective.** *Current Opinion in Investigional Drugs* 6:672-679.

Psychonaut Web Mapping Research Group (2009). **Spice Report.** Institute of Psychiatry, King's College London: London UK.

Rosenbaum CD, Ward JA, Boudreaux ED, Burstein S, and EW (2010). **JWH-018, JWH-073, and Spice. Abstracts of the 2010 International Congress of the European Association of Poison Centres and Clinical Toxicologists, 11-14 May 2010, Bordeaux, France [abstract].** *Clinical Toxicology* 48(3): 240-318.

Schifano F, Corazza 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, and 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(2):137-144.

Schneir AB, Cullen J, and Ly BT (2011). **"Spice" Girls: Synthetic cannabinoid intoxication.** *The Journal of Emergency Medicine* 40(3): 296-299.

Schneir AB, Baumbacher T (2011). **Convulsions Associated with the Use of a Synthetic Cannabinoid Product.** *Journal of Medical Toxicology* Dec 13 2011 Epub.

Seely KA, Prather PL, James LP, and Moran JH (2011). **Marijuana-based synthetic cannabinoids.** *Molecular Interventions* 11(1):37-51.

Simmons J, Cookman L, Kang C, and Skinner C (2011a). **Three cases of "Spice" exposure.** *Clinical Toxicology* 49:431-433.

Simmons JR, Skinner CG, Williams J, Kang CS, Schwartz MD, Wills BK (2011b). **Intoxication from smoking "spice".** *Annals of Emergency Medicine* 57:187-188.

Sobolevsky T, Prasolov I, and Rodchenkov G (2010). **Detection of JWH-018 metabolites in smoking mixture post-administration urine.** *Forensic Science International* 200:141-147.

Solinas M, Panlilio LV, Justinov Z, Yasar S, and Goldberg (2006). **Using drug-discrimination techniques to study the abuse-related effects of psychoactive drugs in rats.** *Nature Protocols* 1(3):1194-1206.

Teske J, Weller J-P, Fieguth A, Rothämel T, Schulz Y, and Tröger HD (2010). **Sensitive and rapid quantification of the cannabinoid receptor agonist napthalen-1-yl-(1-pentylindol-3-yl)methanone (JWH-018) in human serum by liquid chromatography-tandem mass spectrometry.** *Journal of Chromatography B: Biomedical Sciences and Applications* 878(27):2659-2663.

Turu G, Hunyady L. (2010). **Signal transduction of the CB1 cannabinoid receptor.** *Journal of Molecular Endocrinology* 44(2):75-85.

Uchiyama N, Kikura-Hanjiri R, Kawahara N, Haishima Y, and Goda Y (2009). **Identification of a cannabinoid analog as a new type of designer drug in a herbal product.** *Chemistry and Pharmaceutical Bulletin* 57(4):439-441.

Uchiyama N, Kikura-Hanjiri R, Ogata J, and Goda Y (2010a). **Chemical analysis of synthetic cannabinoids as designer drugs in herbal products.** *Forensic Science International* 198:31-38.

Uchiyama N, Kawamura M, Kikura-Hanajiri, and Goda Y (2010b). **Identification of two cannabimimetic phenylacetylindoles JWH-251 and JWH-250, and four cannabimimetic naphthoylindoles JWH-081, JWH-015, JWH-200, and JWH-073 as designer drugs in illegal products.** *Forensic Toxicology*, published online Nov. 5, 2010.

Uchiyama N, Kikura-Hanjiri R, and Goda Y (2011). **Identification of a novel cannabinomimetic phenylacetylindole, cannabipiperidiethanone, as a designer drug in a herbal product and its affinity for cannabinoid CB1 and CB2 receptors.** *Chemical and Pharmaceutical Bulletin (Tokyo)* 59:1203-5.

Vandrey R, Dunn KE, Fry JA, Girling ER (2012). **A survey study to characterize use of Spice products (synthetic cannabinoids)**. *Drug and Alcohol Dependence* 1;120(1-3):238-41.

Vann RE, Warner JA, Bushell K, Huffman JW, Martin BR, Wiley JL (2009). **Discriminative stimulus properties of delta9-tetrahydrocannabinol (THC) in C57Bl/6J mice**. *European Journal of Pharmacology*. 615(1-3):102-7. Epub May 23 2009.

Vardakou I, Pistos C, and Spiliopoulou Ch (2010). **Spice drugs as a new trend: Mode of action, identification and legislation.** *Toxicology Letters* 197(3): 157-162.

Vearrier D and Osterhoudt KC (2010). **A teenager with agitation. Higher than should have climbed.** *Pediatric Emergency Care* 26(6):462-464.

Wachtel SR, ElSohly MA, Ross SA, Ambre J, and de WH (2002). **Comparison of the subjective effects of delta(9)-tetrahydrocannabinol and marijuana in humans.** *Psychopharmacology (Berl)* 161:331-339.

Ward SJ, Mastriani D, Casiano F, and Arnold R (1990). **Pravadoline: Profile in isolated tissue preparations.** *Journal of Pharmacology and Experimental Therapeutics* 255:1230-1239.

Ward SJ (1995). **Aminoalkylindoles: structure-activity relationships of novel cannabinoid mimetics.** *Journal of Medicinal Chemistry* 38(16):3094-3105.

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

Wells DL and Ott CA (2011). **The "new" marijuana.** *The Annals of Pharmacotherapy* 45(3), 414-417.

Wiley JL, Compton DR, Dai D, Lainton JAH, Phillips M, Huffman JW, and Martin BR (1998). **Structure activity relationships of indole- and pyrrole-derived cannabinoids.** *Journal of Pharmacology and Experimental Therapeutics* 285(3):995-1004.

Wintermeyer A, Möller I, Thevis M, Jübner M, Beike J, Rothschild MA, and Bender K (2010). **In vitro phase I metabolism of the synthetic cannabimimetic JWH-018.** *Analytical and Bioanalytical Chemistry* 398(5): 2141-2153.

Yamada K, Rice KC, Flippen-Anderson JL, Eissenstat MA, Ward SJ, Johnson MR, and Howlett AA (1996). **(Aminoalkyl)indole isothiocyanates as potential electrophilic affinity ligands for the brain cannabinoid receptor**. *Journal of Medicinal Chemistry* 39:1967-1974.

Zimmermann US, Winkelmann PR, Pilhatsh M, Nees JA, Spanagel R, and Schulz K (2009). **Withdrawal phenomena and dependence syndrome after consumption of "Spice Gold."** *Deutsches Arzteblatt International* 106(27):464-467.

Zuba D, Byrska B, and Maciow M (2011). **Comparison of "herbal highs" composition.** *Analytical and Bioanalytical Chemistry* 400(1):119-126.