State of Wisconsin
Department of Safety & Professional Services

AGENDA REQUEST FORM

1) Name and Title of Person Submitting the Request:	2) Date When Request Submitted:
Dan Williams	**4/4/13** Items will be considered late if submitted after 4:30 p.m. and less than: ▪ 10 work days before the meeting for Medical Board ▪ 14 work days before the meeting for all others

3) Name of Board, Committee, Council, Sections:

Wisconsin Controlled Substances Board

4) Meeting Date:	5) Attachments:	6) How should the item be titled on the agenda page?
4/25/13	☒ Yes ☐ No	**Follow-up from December-2012 as to UR-144 and XLR-11 / Discussion and Consideration**

7) Place Item in:	8) Is an appearance before the Board being scheduled? If yes, who is appearing?	9) Name of Case Advisor(s), if required:
☒ Open Session ☐ Closed Session ☐ Both	☐ Yes by ☒ No	N/A

10) Describe the issue and action that should be addressed:

MOTION FROM DECEMBER-2012 MEETING:

DISCUSSION AND CONSIDERATION OF SCOPE STATEMENT AS TO THE EMERGENCY SCHEDULING OF CONTROLLED SUBSTANCES

MOTION: Tim Boehmer moved, seconded by Dr. Bloom, to table the discussion and consideration of a scope statement as to the emergency scheduling of controlled substances related to UR-144 and XLR-11 until further information is made available to the Board. Motion carried unanimously.

11) Authorization

Signature of person making this request **Date**

Supervisor (if required) **Date**

Executive Director signature (indicates approval to add post agenda deadline item to agenda) **Date**

Directions for including supporting documents:

1. **This form should be attached to any documents submitted to the agenda.**
2. **Post Agenda Deadline items must be authorized by a Supervisor and the Board Services Bureau Director.**
3. **If necessary, Provide original documents needing Board Chairperson signature to the Executive Assistant prior to the start of a meeting.**

Issued in Washington, DC, on April 4, 2013.

Gary A. Norek,

Manager, Airspace Policy and ATC Procedures Group.

[FR Doc. 2013–08546 Filed 4–11–13; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–373]

Schedules of Controlled Substances: Temporary Placement of Three Synthetic Cannabinoids Into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of Intent.

SUMMARY: The Deputy Administrator of the Drug Enforcement Administration (DEA) is issuing this notice of intent to temporarily schedule three synthetic cannabinoids into the Controlled Substances Act (CSA) pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). The substances are 1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (UR–144), 1-(5-fluoro-pentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoro-UR–144; XLR11) and *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (APINACA, AKB48). This action is based on a finding by the Deputy Administrator that the placement of these synthetic cannabinoids into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. Any final order will be published in the **Federal Register** and may not be issued prior to May 13, 2013. Any final order will impose the administrative, civil, and criminal sanctions and regulatory controls of Schedule I substances under the CSA on the manufacture, distribution, possession, importation, and exportation of these synthetic cannabinoids.

FOR FURTHER INFORMATION CONTACT: John W. Partridge, Executive Assistant, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152, telephone (202) 307–7165.

SUPPLEMENTARY INFORMATION:

Background

Section 201 of the CSA (21 U.S.C. 811) provides the Attorney General with the authority to temporarily place a substance into Schedule I of the CSA for two years without regard to the requirements of 21 U.S.C. 811(b) if he finds that such action is necessary to avoid imminent hazard to the public safety. 21 U.S.C. 811(h). In addition, if proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1), the Attorney General may extend the temporary scheduling up to one year.

Where the necessary findings are made, a substance may be temporarily scheduled if it is not listed in any other schedule under section 202 of the CSA (21 U.S.C. 812) or if there is no exemption or approval in effect under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) for the substance. The Attorney General has delegated his authority under 21 U.S.C. 811 to the Administrator of DEA, who in turn has delegated her authority to the Deputy Administrator of DEA. 28 CFR 0.100, Appendix to Subpart R.

Section 201(h)(4) of the CSA (21 U.S.C. 811(h)(4)) requires the Deputy Administrator to notify the Secretary of the Department of Health and Human Services (HHS) of his intention to temporarily place a substance into Schedule I of the CSA.[1] The Deputy Administrator has transmitted notice of his intent to place UR–144, XLR11, and AKB48 in Schedule I on a temporary basis to the Assistant Secretary by letter dated February 14, 2013. The Assistant Secretary responded to this notice by letter dated March 14, 2013 (received by DEA on March 21, 2013), and advised that based on review by the Food and Drug Administration (FDA), there are currently no investigational new drug applications or approved new drug applications for UR–144, XLR11, or AKB48. The Assistant Secretary also stated that HHS has no objection to the temporary placement of UR–144, XLR11 or AKB48 into Schedule I of the CSA. DEA has taken into consideration the Assistant Secretary's comments. As UR–144, XLR11, and AKB48 are not currently listed in any schedule under the CSA, and as no exemptions or approvals are in effect for UR–144, XLR11, and AKB48 under Section 505 of the FD&C Act (21 U.S.C. 355), DEA believes that the conditions of 21 U.S.C. 811(h)(1) have been satisfied. Any additional comments submitted by the Assistant Secretary in response to this notification shall also be taken into consideration before a final order is published. 21 U.S.C. 811(h)(4).

To make a finding that placing a substance temporarily into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Deputy Administrator is required to consider three of the eight factors set forth in section 201(c) of the CSA (21 U.S.C. 811(c)). These factors are as follows: the substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(c)(4)–(6). Consideration of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

A substance meeting the statutory requirements for temporary scheduling (21 U.S.C. 811(h)(1)) may only be placed in Schedule I. Substances in Schedule I are those that have a high potential for abuse, no currently accepted medical use in treatment in the United States (U.S.), and a lack of accepted safety for use under medical supervision. 21 U.S.C. 812(b)(1). Available data and information for UR–144, XLR11, and AKB48 indicate that these three synthetic cannabinoids have a high potential for abuse, no currently accepted medical use in treatment in the U.S., and a lack of accepted safety for use under medical supervision.

Synthetic Cannabinoids

While synthetic cannabinoids have been developed over the last 30 years for research purposes to investigate the cannabinoid system, no scientific literature referring to UR–144, XLR11 or AKB48 was available prior to these drugs identification in the illicit market. In addition, no legitimate non-research uses have been identified for these synthetic cannabinoids nor have they been approved by FDA for human consumption. These synthetic cannabinoids, of which 1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (UR–144), 1-(5-fluoro-pentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoro-UR–144; XLR11), and *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (APINACA, AKB48) are representative, are so-termed for their Δ^9-tetrahydrocannabinol (THC)—like

[1] Because the Secretary of the Department of Health and Human Services (HHS) has delegated to the Assistant Secretary for Health the Department of Health and Human Services the authority to make domestic drug scheduling recommendations, for purposes of this Notice of Intent, all subsequent references to ''Secretary'' have been replaced with ''Assistant Secretary.'' As set forth in a memorandum of understanding entered into by HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the Controlled Substance Act (CSA), with the concurrence of NIDA. 50 FR 9518.

pharmacological properties. Numerous herbal products have been analyzed, and UR–144, XLR11, and AKB48 have been identified, in varying mixture profiles and amounts, spiked on plant material.

From January 2009 through January 24, 2013, according to the System to Retrieve Information from Drug Evidence (STRIDE) data, there are 1,074 reports involving 137 cases for UR–144, 773 reports involving 134 cases for XLR11, and 66 reports involving 25 cases for AKB48. From March 2010 to January 29, 2013, the National Forensic Laboratory Information System (NFLIS) registered 9,346 reports containing these synthetic cannabinoids (UR–144—4,387 reports; XLR11—4,516 reports; AKB48—443 reports) across 32 states. No instances regarding UR–144, XLR11 or AKB48 were reported in NFLIS prior to March of 2010. Collectively, reports from NFLIS and (STRIDE) [2] (11,259 reports total through January 29, 2013) for UR–144, XLR11 and AKB48 have exceeded the number of reports for the five synthetic cannabinoid substances (JWH–018, JWH–200, JWH–073, CP–47,497 and CP–47,497 C8 homologue [cannabicyclohexanol]) (7,340 total reports through December 31, 2012). JWH–018, JWH–200, JWH–073, CP–47,497 and CP–47,497 C8 homologue were temporarily scheduled on March 1, 2011, and later placed in Schedule I by Section 1152 of Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112–144, on July 9, 2012. Section 1152 of the FDASIA [3] amended the CSA by placing cannabimimetic agents and 26 specific substances (including 15 synthetic cannabinoids, 2 synthetic cathinones, and 9 phenethylamines of the 2C-series) in Schedule I. UR–144, XLR11, and AKB48 were not included among the 15 specific named synthetic cannabinoids, and do not fall under the definition of cannabimimetic agents, under FDASIA.

Factor 4. History and Current Pattern of Abuse

Synthetic cannabinoids laced on plant material were first reported in the U.S. in December 2008, when a shipment of 'Spice' was seized and analyzed by U.S. Customs and Border Patrol in Dayton, Ohio. Also in December 2008, JWH–018 and cannabicyclohexanol were identified by German forensic laboratories.

Since the initial identification of JWH–018 (December 2008), many additional synthetic cannabinoids with purported psychotropic effects have been found laced on plant material or related products. The popularity of these synthetic cannabinoids and their associated products appears to have increased since January 2010 in the U.S. based on seizure exhibits and media reports. This trend appears to mirror that experienced in Europe since 2008. Synthetic cannabinoids are being encountered in several regions of the U.S. with the substances primarily found as adulterants on plant material products as self-reported on internet discussion boards. Since then, numerous other synthetic cannabinoids including UR–144, XLR11 and AKB48 have been identified as product adulterants.

Data gathered from published studies, supplemented by discussions on Internet discussion Web sites and personal communications with toxicological testing laboratories, demonstrate that products laced with UR–144, XLR11 and/or AKB48 are being abused mainly by smoking for their psychoactive properties. The adulterated products are marketed as 'legal' alternatives to marijuana. This characterization, along with their reputation as potent herbal intoxicants, has increased their popularity. Several synthetic cannabinoids have been shown to display higher potency in vitro when compared to THC. Smoking mixtures of these substances for the purpose of achieving intoxication has been identified as a reason for numerous emergency room visits and calls to poison control centers. Abuse of these synthetic cannabinoids and their products has been characterized with both acute and long term public health and safety issues. In addition, numerous states, local jurisdictions, and the international community have controlled these substances.

Factor 5. Scope, Duration and Significance of Abuse

According to forensic laboratory reports, the first appearance of synthetic cannabinoids in the U.S. occurred in November 2008, when U.S. Customs and Border Protection analyzed ''Spice'' products. NFLIS has reported 9,346 exhibits (March 2010 to January 29, 2013) related to UR–144, XLR11 and AKB48 from various states including Alaska, Alabama, Arkansas, California, Colorado, Florida, Georgia, Iowa, Indiana, Illinois, Kansas, Kentucky, Louisiana, Maryland, Minnesota, Missouri, New Hampshire, New Jersey, New Mexico, North Dakota, Nebraska, Nevada, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Virginia, Wisconsin and Wyoming. STRIDE has reported 1,913 records involving UR–144, XLR11 and AKB48 from January 2009 through January 24, 2013. From January 1 through December 31, 2012, the American Association of Poison Control Centers [4] has reported receiving in excess of 5,200 calls relating to products purportedly laced with synthetic cannabinoids. Although the center does not identify specific cannabinoid substances, the data does indicate the magnitude of exposure to synthetic cannabinoids.

Factor 6. What, If Any, Risk There Is to the Public Health

UR–144, XLR11 and AKB48 are pharmacologically similar to Schedule I substances THC and JWH–018, as well as other synthetic cannabinoids. By sharing pharmacological similarities with the Schedule I substances (THC and JWH–018), synthetic cannabinoids pose a risk to the abuser. In addition, the chronic abuse of products laced with synthetic cannabinoids has also been linked to addiction and withdrawal. Law enforcement, military, and public health officials have reported exposure incidents that demonstrate the dangers associated with abuse of synthetic cannabinoids to both the individual abusers and other affected individuals since these substances were never intended for human use. Warnings regarding the dangers associated with abuse of synthetic cannabinoids and their products have been issued by numerous state public health departments and poison control centers and private organizations. In a 2012 report, the Substance Abuse and Mental Health Services Administration [5] reported 11,406 emergency department visits involving a synthetic cannabinoid product during 2010.

Detailed product analyses have detected variations in the amount and type of synthetic cannabinoid laced on plant material even within samplings of

[2] National Forensic Laboratory Information System (NFLIS) is a program sponsored by Drug Enforcement Administration's (DEA) Office of Diversion Control which compiles information on exhibits analyzed in State and local law enforcement laboratories. System to Retrieve Information from Drug Evidence (STRIDE) is a DEA database which compiles information on exhibits analyzed in DEA laboratories.

[3] Subtitle D of Title XI of the Food and Drug Administration Safety and Innovation Act (FDASIA), which includes Sections 1151–1153 of Pub. L. 112–144, is also known as the ''Synthetic Drug Abuse Prevention Act of 2012,'' or ''SDAPA.''

[4] American Association of Poison Control Centers (AAPCC) is a non-profit, national organization that represents the poison centers of the United States.

[5] Substance Abuse and Mental Health Services Administration (SAMHSA) is a branch of the U.S. Department of Health and Human Services (HHS). It is charged with improving the quality and availability of prevention, treatment, and rehabilitative services in order to reduce illness, death, disability, and cost to society resulting from substance abuse and mental illnesses.

the same product. Since abusers obtain these drugs through unknown sources, purity of these drugs is uncertain, thus posing significant adverse health risk to these users. Submissions to DEA laboratories from January 2012 through February 11, 2013, have documented over 142 distinct packaging examples containing a mixture of UR–144, XLR11 and/or AKB48. These unknown factors present a significant risk of danger to the abuser. Some of the adverse health effects reported in response to the abuse of synthetic cannabinoids include vomiting, anxiety, agitation, irritability, seizures, hallucinations, tachycardia, elevated blood pressure, and loss of consciousness. As mentioned above, there are reported instances of emergency department admissions in association with the abuse of these THC-like substances. There are no recognized therapeutic uses of these substances in the U.S.

In February 2013, the Centers for Disease Control and Prevention published a report by Murphy et al. describing unexplained cases of acute kidney injury in 16 patients, all of whom had reported recent smoking of synthetic cannabinoids. Upon further investigation, it was determined that of the 16 patients, 7 of the subjects had smoked substances that were positive for XLR11 or its metabolite. Cases were reported from Wyoming (4 cases), Rhode Island (1 case), New York (2 cases), Oregon (6 cases), Kansas (1 case) and Oklahoma (2 cases).

Finding of Necessity of Schedule I Scheduling To Avoid Imminent Hazard to Public Safety

Based on the above data and information, the continued uncontrolled manufacture, distribution, importation, exportation, and abuse of UR–144, XLR11, and AKB48 pose an imminent hazard to the public safety. DEA is not aware of any currently accepted medical uses for these synthetic cannabinoids in the U.S. A substance meeting the statutory requirements for temporary scheduling (21 U.S.C. 811(h)(1)) may only be placed in Schedule I. Substances in Schedule I are those that have a high potential for abuse, no currently accepted medical use in treatment in the U.S., and a lack of accepted safety for use under medical supervision. Available data and information for UR–144, XLR11, and AKB48 indicate that these three synthetic cannabinoids have a high potential for abuse, no currently accepted medical use in treatment in the U.S., and a lack of accepted safety for use under medical supervision. As required by section 201(h)(4) of the CSA (21 U.S.C. 811(h)), the Deputy Administrator through a letter dated February 14, 2013, notified the Assistant Secretary of Health of the intention to temporarily place these three synthetic cannabinoids in Schedule I.

Conclusion

This notice of intent initiates expedited temporary scheduling action and provides the 30-day notice pursuant to section 201(h) of the CSA (21 U.S.C. 811(h)). In accordance with the provisions of section 201(h) of the CSA (21 U.S.C. 811(h)), the Deputy Administrator has considered available data and information and has set forth herein the grounds for his determination that it is necessary to temporarily schedule three synthetic cannabinoids, 1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (UR-144), 1-(5-fluoro-pentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoro-UR-144; XLR11), and *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (APINACA, AKB48) in Schedule I of the CSA and finds that placement of these synthetic cannabinoids into Schedule I of the CSA is warranted in order to avoid an imminent hazard to the public safety.

Because the Deputy Administrator hereby finds that it is necessary to temporarily place these synthetic cannabinoids into Schedule I to avoid an imminent hazard to the public safety, any subsequent final order temporarily scheduling these substances will be effective on the date of publication in the **Federal Register**, and will be in effect for a period of up to three years pending completion of the permanent or regular scheduling process. It is the intention of the Deputy Administrator to issue such a final order as soon as possible after the expiration of 30 days from the date of publication of this notice. UR–144, XLR11, and AKB48 will then be subject to the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, possession, importing and exporting of a Schedule I controlled substance under the CSA.

Regular scheduling actions in accordance with 21 U.S.C. 811(a) are subject to formal rulemaking procedures done ''on the record after opportunity for a hearing'' conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth specific criteria for scheduling a drug or other substance. While temporary scheduling orders are not subject to judicial review (21 U.S.C. 811(h)(6)), the regular scheduling process of formal rulemaking affords interested parties with appropriate process and the government with any additional relevant information needed to make a determination. Final decisions which conclude the regular scheduling process of formal rulemaking are subject to judicial review. 21 U.S.C. 877.

Regulatory Matters

Section 201(h) of the CSA (21 U.S.C. 811(h)) provides for an expedited temporary scheduling action where such action is necessary to avoid an imminent hazard to the public safety. As provided in this subsection, the Attorney General may, by order, schedule a substance in schedule I on a temporary basis. Such an order may not be issued before the expiration of 30 days from (1) the publication of a notice in the **Federal Register** of the intention to issue such order and the grounds upon which such order is to be issued, and (2) the date that notice of a proposed temporary scheduling order is transmitted to the Secretary of HHS. 21 U.S.C. 811(h)(1).

Inasmuch as section 201(h) of the CSA directs that temporary scheduling actions be issued by order and sets forth the procedures by which such orders are to be issued, DEA believes that the notice and comment requirements of section 553 of the Administrative Procedure Act (APA) (5 U.S.C. 553) do not apply to this notice of intent. In the alternative, even assuming that this notice of intent might be deemed to be subject to section 553 of the APA, the Deputy Administrator finds that there is good cause to forgo the notice and comment requirements of section 553, as any further delays in the process for issuance of temporary scheduling orders would be impracticable and contrary to the public interest in view of the manifest urgency of the temporary scheduling action to avoid an imminent hazard to the public safety.

Although this notice of intent to issue a temporary scheduling order is not subject to the notice and comment requirements of section 553 of the APA, DEA notes that in accordance with 21 U.S.C. 811(h)(4), the Deputy Administrator will be taking into consideration any comments submitted by the Secretary of HHS with regard to the proposed temporary scheduling order. Further, DEA believes that this temporary scheduling action is not a ''rule'' as defined by 5 U.S.C. 601(2), and, accordingly, not subject to the requirements of the Regulatory Flexibility Act. The requirements for the preparation of an initial regulatory flexibility analysis in 5 U.S.C. 603(a) are not applicable where (as here) the agency is not required by section 553 of

the APA or any other law to publish a general notice of proposed rulemaking.

Additionally, this action is not a significant regulatory action as defined by Executive Order 12866 ''Regulatory Planning and Review'', section 3(f), and, accordingly, this action has not been reviewed by the Office of Management and Budget.

This action will not have substantial direct effects on the States, on the relationship between the national government and the States, or on distribution of power and responsibilities among the various levels of government. Therefore, in accordance with Executive Order 13132 ''Federalism'' it is determined that this action does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

Under the authority vested in the Attorney General by section 201(h) of the CSA (21 U.S.C. 811(h)), and delegated to the Deputy Administrator of the DEA by Department of Justice regulations (28 CFR 0.100, Appendix to Subpart R), the Deputy Administrator hereby intends to order that 21 CFR Part 1308 be amended as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

■ 1. The authority citation for Part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

■ 2. Section 1308.11 is amended by adding new paragraphs (h)(9), (10), and (11) to read as follows:

§ 1308.11 Schedule I.

* * * * *

(h) * * *

(9) 1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone, its optical, positional, and geometric isomers, salts and salts of isomers—7144 (Other names: UR-144, 1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole)

(10) 1-(5-fluoro-pentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone, its optical, positional, and geometric isomers, salts and salts of isomers—7011 (Other names: 5-fluoro-UR-144, 5-F-UR-144, XLR11, 1-(5-fluoro-pentyl)-3-(2,2,3,3-tetramethylcyclopropoyl)indole)

(11) *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide, its optical, positional, and geometric isomers, salts and salts of isomers—7048 (Other names: APINACA, AKB48)

Dated: April 5, 2013.

Thomas M. Harrigan,

Deputy Administrator.

[FR Doc. 2013–08671 Filed 4–11–13; 8:45 am]

BILLING CODE 4410–09–P

DEPARTMENT OF THE INTERIOR

Bureau of Indian Affairs

25 CFR Part 170

[BY–/AM65P0002.99900/]

Tribal Consultation on the Draft Regulations Governing the Tribal Transportation Program

AGENCY: Bureau of Indian Affairs, Interior.

ACTION: Notice of Tribal Consultations and Informational Meetings.

SUMMARY: The Bureau of Indian Affairs is announcing tribal consultations to discuss draft revisions of the regulations governing the Tribal Transportation Program. The consultations will also cover requirements for proposed roads and access roads to be included in the National Tribal Transportation Facility Inventory and will include an update regarding the ongoing quality assurance review of the facility inventory.

DATES: Comments on the draft rule are due by June 14, 2013. The consultation sessions will be held on the following dates, at the following locations:

Meeting date	Location	Time
May 14, 2013	Anchorage, AK	9 a.m.–4:30 p.m.
May 16, 2013	Phoenix, AZ	9 a.m.–4:30 p.m.
May 21, 2013	Minneapolis, MN	9 a.m.–4:30 p.m.

ADDRESSES:

• *Send comments to:* LeRoy M. Gishi, Chief, Division of Transportation, Bureau of Indian Affairs, 1849 C Street, NW., MS–4513, Washington, DC 20240, telephone (202) 513–7711, email: *leroy.gishi@bia.gov*; or Robert W. Sparrow, Jr., Director, Tribal Transportation Program, Federal Highway Administration, 1200 New Jersey Ave, SE., Room E61–311, Washington, DC 20159, telephone (202) 366–9483, email: *robert.sparrow@dot.gov*.

• Addresses of the venues at which each meeting will be held, a copy of the draft regulation, and background information are posted at the following Web site (the address is case-sensitive, please use capitals where indicated): *http://www.bia.gov/WhoWeAre/BIA/OIS/Transportation.*

FOR FURTHER INFORMATION CONTACT: LeRoy M. Gishi, telephone (202) 513–7711; email: *leroy.gishi@bia.gov*; or Robert W. Sparrow, Jr., telephone (202) 366–9483; email: *robert.sparrow@dot.gov*.

SUPPLEMENTARY INFORMATION: Federally recognized tribes are invited to attend one or more of the consultation and informational sessions regarding the following topics:

• On July 6, 2012, Moving Ahead for Progress in the 21st Century Act (MAP–21), Public Law 112–141, a two-year reauthorization of the transportation act, was signed into law by President Obama and became effective on October 1, 2012.

• Section 1119 of MAP–21 struck the existing laws governing the Indian Reservation Roads Program from 23 U.S.C. 201–204, and renumbered many of those sections under 23 U.S.C. 201 and 202 and changed the name from ''Indian Reservation Roads Program'' to ''Tribal Transportation Program (TTP).'' MAP–21 also changed the name of the ''Indian Reservation Roads Inventory'' to the ''National Tribal Transportation Program Facility Inventory (NTTFI).'' *See* 23 U.S.C. 202(b)(1). Section 1103 of MAP–21 amended the name of an ''Indian Reservation Road'' to a ''Tribal Transportation Facility.''

• Section 1119 of MAP–21 created a new formula for distribution of TTP funds among tribes, which had the effect of overriding the existing Relative Need Distribution Formula (RNDF) that was published in 2004 at 25 CFR part 170, Subpart C. *See* 23 U.S.C. 202(b)(3). Although the RNDF is no longer applicable under the new TTP formula, certain historical aspects of the former

1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole (UR-144), 1-(5-fluoro-pentyl)-3-(2,2,3,3-tetramethylcyclopropoyl)indole (5-fluoro-UR-144; XLR11) and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA, AKB48)

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

Drug and Chemical Evaluation Section, Office of Diversion Control, Drug Enforcement Administration, Washington, DC 20537

April 2013

Introduction

Since 2009, there has been a marked increase in the law enforcement encounters of various synthetic cannabinoids in the United States. Both law enforcement and public health reports suggest the sustained popularity of these substances in the designer drug market, most commonly abused as plant material adulterants. These associated products are often being sold as incense and labeled 'not for human consumption'. Additionally, these products are marketed as a 'legal high' or 'legal alternative to marijuana' and are readily available over the internet, in head shops, or sold in convenience stores.

These substances have no accepted medical use in the United States and have been reported to produce adverse effects in humans. Chronic abuse of synthetic cannabinoids in general has been linked to adverse health effects including signs of addiction and withdrawal (Zimmermann et al., 2009; Muller et al., 2010), as well as numerous reports of emergency room admissions resulting from their abuse (Forrester et al., 2011; Hermanns-Clausen et al., 2012, SAMHSA, 2012).

1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole (UR-144), 1-(5-fluoro-pentyl)-3-(2,2,3,3-tetramethylcyclopropoyl)indole (5-fluoro-UR-144; XLR11) and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA, AKB48) are synthetic cannabinoids (Figure 1) and are pharmacologically similar to the Schedule I hallucinogen *delta*-9-tetrahydrocannabinol (Δ^9-THC). UR-144 was first developed as a research tool by Abbott laboratories (Frost et al., 2010). XLR11 and AKB48 were not designed as research tools, however began showing up in seizures as early as 2009. From January 2009 through April 03, 2013 according to the System to Retrieve Information on Drug

Evidence (STRIDE[1]) data, there are 1,510 reports involving 179 cases for UR-144, 1,194 reports involving 186 cases for XLR11 and 112 reports involving 40 cases for AKB48. From March 2010 to January 29, 2013, the National Forensic Laboratory Information System (NFLIS[2]) registered 13,956 reports containing these synthetic cannabinoids (UR-144 – 5,356 reports; XLR11 – 8,075 reports; AKB48 – 525 reports) across 32 states. No reports regarding UR-144, XLR11 or AKB48 were reported in NFLIS prior to March of 2010.

Collectively, NFLIS and STRIDE reports (13,956 reports total through April 03, 2013) for UR-144, XLR11 and AKB48 have exceeded the number of reports encountered all time for the five synthetic cannabinoid substances (JWH-018, JWH-200, JWH-073, CP-47,497 and CP-47,497 C8 homologue [cannabicyclohexanol]) (7,512 total reports through April 03, 2013) temporarily scheduled on March 1, 2011 and later placed in Schedule I on July 9, 2012 by the Food and Drug Administration Safety and Innovation Act (FDASIA)[3]. Pub. L. 112-144. Section 1152 of the FDASIA amended the Controlled Substances Act (CSA) by placing 26 specific substances (including 15 synthetic cannabinoids, 2 synthetic cathinones, and 9 phenethylamines of the 2C-series) in Schedule I. UR-144, XLR11 and AKB48 were not captured under the FDASIA.

With no legitimate medical use and limited pharmacological information, these substances (UR-144, XLR11 and AKB48) have emerged on the designer drug market and are being abused for their psychoactive properties. To protect the public health and safety, the Drug Enforcement Administration (DEA) intends to temporarily place UR-144, XLR11 and AKB48 in Schedule I of the Controlled Substances Act (CSA). With respect to finding an imminent hazard to the public safety, DEA has considered the factors required under the CSA for the temporary scheduling of UR-144, XLR11 and AKB48. 21 U.S.C. 811(h)(3) and 811(c)(4)-(6).

[1] STRIDE, a DEA database which compiles information on exhibits analyzed in DEA laboratories.
[2] NFLIS, a DEA database which compiles information on exhibits analyzed in state and local laboratories.
[3] Sections 1151-1153 of the FDASIA are also known as the "Synthetic Drug Abuse Prevention Act of 2012" (SDAPA).

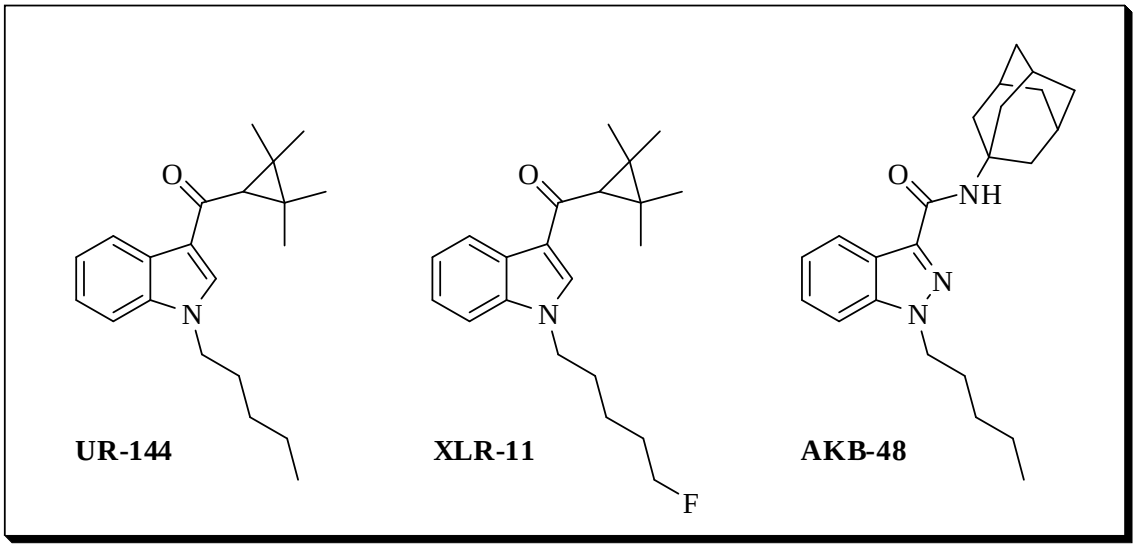

Figure 1. Chemical Structures

UR-144 and XLR11 are classified as cyclopropylindoles, a class of compounds that have previously been investigated due to their possible cytotoxic, anti-cancer or anti-HIV potentials (Wang et al., 1996, Milbank et al., 1999, Sharma et al., 2001, Choi and Ma, 2010, Hassam, 2012) as well as their affinity for cannabinoid receptors (Frost et al., 2010). Currently available data for UR-144 include binding (Frost et al., 2010, Perkin Elmer, 2013; RTI, 2013) locomotor (Elsken et al., 2013) and drug discrimination (RTI, 2013) data (Table 1). Similarly, currently available data for XLR11 include binding and drug discrimination data (RTI, 2013), a functional assay test (Perkin Elmer et al., 2013) and locomotor data (Elsken et al, 2013; Table 1). AKB48 is classified as a pentyl indazole and has been reported in the literature as a cannabinoid agonist (Uchiyama, 2012a, Uchiyama et al., 2012b). To date, AKB48 has been evaluated in in vitro binding and functional assays and in locomotor study (Elsken et al., 2013, Perkin Elmer, 2013; Table 1).

Synthetic Cannabinoids

1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole (UR-144)

UR-144 has been shown to bind to both the CB1 and CB2 receptors (Frost et al., 2010; RTI, 2013). A study conducted by contract researchers of the National Institute on Drug Abuse (NIDA) and of the DEA indicated that UR-144 is an agonist at CB1 and CB2 receptors (Perkin Elmer, 2013; RTI, 2013). UR-144 (ED_{50} = 7.1 µmol/kg) has been shown to

be THC-like in drug discrimination studies (RTI, 2013). A NIDA study evaluating locomotor effects of UR-144 concluded that treatment with UR-144 resulted in both time- and dose-dependent depression of locomotor activity following 10 and 30 mg/kg (Elsken et al., 2013). UR-144 is chemically similar to other Schedule I substances such as JWH-018 and AM-2201. These substances (UR-144, AM-2201 and JWH-018) share the same core indole structure with substitutions at the 1 and 3 positions of this fused bicyclic ring system. They bind to CB1 receptors, and are substances representative of the aminoalkylindole structural class. Numerous substances of the aminoalkylindole class have been shown to exhibit typical cannabinoid pharmacology *in vivo* (D'Ambra et al., 1992; Compton et al., 1992a).

1-(5-fluoro-pentyl)-3-(2,2,3,3-tetramethylcyclopropoyl)indole (5-fluoro-UR-144; XLR11)

XLR11 was first identified in 2012 as an ingredient in synthetic cannabis smoking blends. XLR11, similar to JWH-018, is a substance representative of the aminoalkylindole structural class. Numerous substances of the aminoalkylindole class are known to exhibit CB1 cannabinoid pharmacology *in vivo* (D'Ambra et al., 1992, Compton et al., 1992a). The cyclopropylindole XLR11, also known as 5-fluoro-UR-144, closely resembles UR-144 in that it retains the identical core structure. A fluorine group is added to the end of the side chain attached to the 1-position of the indole core. While XLR11 shows structural similarity to UR-144, JWH-018, AM-2201, A-796,260 and A-834,735, it was not listed in any patent or scientific literature alongside these compounds and does not appear to have been produced by Abbott Laboratories. The structure-activity relationship information indicates that the substitution of a fluoride atom on the terminal position of the five carbon alkyl chain (pentyl) (Example AM-2201 vs. JWH-018) is well-tolerated. Thus, it is anticipated that the substitution of a fluoride atom on the alkyl chain of UR-144, as is the case with XLR11, would retain similar binding affinity for the CB1 receptor. Structure-activity relationship studies indicate that indole derivatives substituted with an alkyl group at the indole-1 position retain activity at the cannabinoid receptors (Huffman, 1994; Wiley et al., 1998, Aung et al., 2000) and replacement of the naphthyl group by a tetramethylcyclopropyl also retains activity at the cannabinoid receptors (Frost et al., 2010). XLR11, similar to JWH-018, has the above-mentioned substitutions at the indole-1 and indole-3 positions.

XLR11 has been shown to bind to both the CB1 and CB2 receptors (RTI, 2013). A study conducted by contract researchers of the National Institute on Drug Abuse (NIDA) and of the DEA indicated that XLR11 is an agonist at CB1 and CB2 receptors (Perkin Elmer, 2013; RTI, 2013). XLR11 (ED_{50} = 3.3 µmol/kg) has been shown to be THC-like in drug discrimination studies (RTI, 2013). A study by the contract researchers of the NIDA

found that XLR11 (10 and 30 mg/kg) suppresses locomotor activity in both time- and dose-dependent manner (Elsken et al., 2013). A report by the Centers for Disease Control and Prevention (CDC) in February of 2013 described 16 patients that presented to emergency departments with nausea, vomiting, abdominal pain and acute kidney injury following smoking of synthetic cannabinoids (Murphy et al., 2013). Of these 16 patients, toxicological analysis of product samples and clinical specimens identified XLR11 or its metabolite in 7 of the 16 patients.

N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA, AKB48)

The pentyl indazole AKB48, also referred to as APINACA, is expected have a potent affinity for both the CB1 and CB2 receptors based upon data that show confirmed analogs of AKB48, differing only by the addition of a functional group (Cl-, I- or CN- group substituted for the terminal methyl of the pentyl moiety) have a very high affinity for the cannabinoid receptors. Three compounds referred to as analogs for AKB48 had reported K_i values of 1.7, 0.6 and 2.3 nM for the CB1 receptor (Makriyannis, 2003) (Uchiyama, 2012a). AKB48 has been shown to bind to both the CB1 and CB2 receptors (RTI, 2013; Uchimaya et al., 2012b). A study conducted by contract researchers of the National Institute on Drug Abuse (NIDA) indicated that AKB48 is an agonist at CB1 receptors (Perkin Elmer, 2013). First identified in Japan in March of 2012 as an ingredient in synthetic cannabis smoking blends (Uchiyama et al., 2012b), AKB48 closely resembles cannabinoid compounds outlined in patent WO 2003/035005 (Makriyannis, 2003). AKB48 is structurally similar to JWH-018 with AKB48 containing a pentyl chain on the indazole-1 position. A drug discrimination study demonstrated that JWH-018 fully substitutes for THC at 3 mg/kg (Jarbe et al., 2011). JWH-018 was also reported to suppress the locomotor activity of rats with greater significance and for longer duration than Δ^9-THC (Uchiyama et al., 2012c), suggesting that AKB48 may have cannabimimetic activity similar to that of JWH-018 (Uchiyama, 2012a). A study by the contract researchers of NIDA found that AKB48 (3 to 30 mg/kg) reduces locomotor activity in both time- and dose-dependent manner (Elsken et al., 2013).

Table 1. Summary of Available Pharmacology Data for UR-144, XLR11 and AKB48

	In vivo		*In vitro*	
	Binding at CB1	Function at CB1	Locomotor Activity (8-hr session)	THC Drug Discrimination
UR-144	K_i = 28.9 nM[A] K_i = 150 nM[I]	Agonist EC_{50} = 1295 nM[B]	Depressed (ID_{50}=7.8 mg/kg)[F]	Full Substitution (ED_{50} = 7.1 µmol/kg[A])
XLR11	K_i = 24.2 nM[A]	Agonist EC_{50} = 359 nM[C]	Depressed (ID_{50}=10.3 mg/kg)[G]	Full Substitution (ED_{50} = 3.3 µmol/kg[A])
AKB48	K_i = 304.5 nM[D]	Agonist EC_{50} = 585 nM[E]	Depressed (ID_{50}=2.2 mg/kg)[H]	NC

[A] RTI International, 2013
[B] Perkin Elmer, 2013a
[C] Perkin Elmer, 2013b
[D] Perkin Elmer, 2013c
[E] Perkin Elmer, 2013d
[F] Elsken et al., 2013a
[G] Elsken et al., 2013b
[H] Elsken et al., 2013c
[I] Frost et al., 2010
NC – not completed

Factor 4. Its history and current pattern of abuse

Synthetic cannabinoids were 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. Additionally around the same time, in December 2008, JWH-018 and cannabicyclohexanol were identified by German forensic laboratories (EMCDDA, 2009). It has been stated that there is a belief that these substances existed and were abused some time prior to their identification (Psychonaut Web Mapping Research Group, 2009).

Since the initial identification of JWH-018 (December 2008), many additional synthetic cannabinoids have been found laced on related products (Auwarter et al., 2009, DEA, 2009). The popularity of these cannabimimetic substances and their associated products appears to have increased since January 2010 in the United States based on seizure exhibits and media reports. This trend appears to mirror those experienced in Europe since 2008 (EMCDDA, 2009). Synthetic cannabinoids are being encountered in most regions of the U.S. with the substances found as adulterants on plant material or being abused alone as self-reported on internet discussion boards (Atwood et al., 2010).

Data gathered from published studies, supplemented by discussions on Internet discussion websites and personal communications demonstrate that these products are being abused mainly by smoking for their psychoactive properties. The adulterated products are marketed as 'legal' alternatives to marijuana. 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. Several synthetic cannabinoids have been shown to display higher potency *in vitro* and *in vivo* when compared to Δ^9-THC (Compton et al., 1992a, Wiley et al., 1998). Smoking mixtures of these substances abused for the purpose of achieving intoxication have resulted in numerous emergency room visits and calls to poison control centers. Abuse of these synthetic cannabinoids and their products has been characterized with both acute and long term public health and safety issues. Numerous states, local jurisdictions, and the international community have also controlled these substances.

Synthetic cannabinoids have been developed over the last 30 years to be used as tools for investigating the cannabinoid system (Weissman et al., 1982; Huffman et al., 1996; Huffman et al., 1999). Subsequently, these substances have been identified as adulterants in numerous retail products (Auwarter et al., 2009, EMCDDA, 2009, Lindigkeit et al., 2009, Dresen et al., 2010, Hudson et al., 2010, Uchiyama et al., 2010, Uchiyama, 2012a, Uchiyama et al., 2012b). JWH-018 was the first synthetic cannabinoid to be identified as a product adulterant in Germany in 2008. This substance was initially synthesized as a research tool to investigate the cannabinoid system (Huffman, 1994, Wiley et al., 1998). Since then, numerous other synthetic cannabinoids including UR-144, XLR11 and AKB48 have been identified as product adulterants and bulk seizures have occurred by law enforcement. NFLIS details over 13,956 reports from forensic laboratories identifying UR-144, XLR11 and AKB48 in drug related reports for a period from March 2010 to April 03, 2013. In addition, STRIDE has 2,816 reports involving UR-144, XLR11 and AKB48 from January 2009 through April 03, 2013.

Youth appear to be the primary abusers of synthetic cannabinoids and synthetic cannabinoid-containing products, as supported by law enforcement encounters and reports from emergency rooms (SAMHSA, 2012)[4]; however, all age groups have been discussed in media reports as abusing these substances and related products. For patients between the ages of 12-29, 78% of emergency department visits in 2010 involved synthetic cannabinoids. In addition, the majority (59%) of emergency department visits of patients aged 12 to 29 did not involve any other substance. Of the remaining 41% of individuals, the most frequently abused substance in combination with synthetic cannabinoids was marijuana (17%), pharmaceuticals (17%) and alcohol (13%) (SAMHSA, 2012). Individuals including minors are purchasing synthetic cannabinoids from Internet websites, gas stations, convenience stores, and head shops. These substances and laced products are commonly marketed as 'legal highs' with a disclaimer of 'not for human consumption'. As detailed in reports, law enforcement and public health officials are encountering the abuse of these substances (Murphy et al., 2013, NFLIS, 2013, STRIDE, 2013).

Numerous herbal incense products have been found to contain one or more synthetic cannabinoid(s) (UR-144, XLR11 and/or AKB48) laced on plant material (Appendix 1). 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 (Auwarter et al., 2009, EMCDDA, 2009, Atwood et al., 2010). To lace the plant material, the synthetic cannabinoids are generally dissolved in a solvent and sprayed on the plant material or the plant material is soaked in a solution of the dissolved substance (Vardakou et al., 2010, Wells and Ott, 2011). Two research articles propose that the packaging is professional and inconspicuous (unlabeled), targeting young people, possibly eager to use cannabis, but who are afraid of the judicial consequences and/or association with illicit drugs (Lindigkeit et al., 2009, Schifano, 2009).

Dresen and colleagues (Dresen et al., 2010) found that synthetic cannabinoids are being abused by individuals in drug treatment centers with a positive rate of 63.3% in forensic psychiatric centers based on their sampling. U.S. Drug Courts[5] have

[4] SAMHSA is a branch of the U.S. Department of Health and Human Services. It is charged with improving the quality and availability of prevention, treatment, and rehabilitative services in order to reduce illness, death, disability, and cost to society resulting from substance abuse and mental illnesses.
[5] Drug courts were developed to achieve a reduction in recidivism and substance abuse among nonviolent, substance abusing offenders by increasing their likelihood for successful rehabilitation through early, continuous, and intense judicially supervised treatment, mandatory periodic drug testing, and the use of

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 (information communicated to DEA).

As part of the Monitoring the Future (MTF)[6] Report for 2012, some of the most important findings were presented in a press release on December 19, 2012. In this press release, the MTF study detailed that while synthetic cannabinoid use has remained level in 12th graders at 11.3%, "the fact that its prevalence rate has remained high despite federal and state efforts to reduce its use is troublesome" (Johnston et al., 2012). For the first time, synthetic cannabinoid use in 8th and 10th graders was measured, with annual prevalence rates being 4.4% and 8.8% respectively.

Summary

Recently, law enforcement has been encountering UR-144, XLR11 and AKB48 and their products in increasing numbers. Synthetic cannabinoids and their associated products are available over the Internet or found to be sold in gas stations, convenience stores, and tobacco and head shops. UR-144, XLR11 and AKB48, similar to the previously scheduled synthetic cannabinoids (DEA, 2012), have been seized alone and spiked on products that are marketed as herbal incense and promoted as legal alternatives to marijuana.

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

NFLIS, a national database capturing data from forensic laboratories, has reported 13,956 reports (March 2010 to January 29, 2013) related to UR-144, XLR11 and AKB48 from various states including, Alaska, Alabama, Arkansas, California, Colorado, Florida, Georgia, Iowa, Indiana, Illinois, Kansas, Kentucky, Louisiana, Maryland, Minnesota, Missouri, New Hampshire, New Jersey, New Mexico, North Dakota, Nebraska, Nevada, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Virginia, Wisconsin and Wyoming (query date: January 29, 2013). STRIDE has 2,816 reports involving UR-144, XLR11 and AKB48 from January 2009 through April 03, 2013 (query date: April 04, 2013). Recently, increased exposure incidents have been documented by poison control centers in the United States as the abuse of synthetic cannabinoids has been associated with both acute and long-term public health and safety concerns. From January 1 through December 31, 2012, the American Association

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appropriate sanctions and other rehabilitation services. Drug courts analyze specimens from participants for new and existing drugs of abuse.

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

of Poison Control Centers (AAPCC) has reported receiving an excess of 5,200 exposure calls corresponding to products purportedly laced with synthetic cannabinoids, although the data provided does not generally include biological sample testing that would confirm which cannabinoids the user was exposed to[7]. In addition, AAPCC has reported over 400 calls regarding synthetic cannabinoids through February of 2013. A majority of exposure incidents resulted in seeking medical attention at health care facilities. Chronic abuse of synthetic cannabinoids has been linked to signs of addiction and withdrawal similar to that experienced with cannabis abuse (Zimmermann et al., 2009, Muller et al., 2010, Vardakou et al., 2010). Additionally, tolerance to these drugs may develop fairly rapidly with larger doses being required to achieve the desired effect (EMCDDA, 2009). In 2010, the Substance Abuse and Mental Health Services Administration (SAMHSA) reported 11,406 emergency department visits involved a synthetic cannabinoid product. In 2011, SAMHSA reported the number of emergency department visits involving a synthetic cannabinoid product had increased 2.5 times to 28,531 (SAMHSA, 2013) (Figure 1).

Synthetic cannabinoids and the associated products are sold over the Internet and found to be abused by diverse populations. Since synthetic cannabinoids 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). The scientific literature and reports received by DEA suggest that tolerance and dependence to synthetic cannabinoids may develop (Zimmermann 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 UR-144, XLR11 and AKB48, evident from the increasing number of encounters reported by forensic laboratories (NFLIS data). The initial indication of the evidence of abuse of AKB48 appeared in 2011 upon identification in products, with evidence of abuse of UR-144 and XLR11 appearing in 2012. Due to the previous temporary scheduling action of

[7] 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 Control Centers (PCCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g. an ingestion, inhalation, 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 PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

the five synthetic cannabinoids (JWH-018, JWH-200, JWH-073, CP-47,497 and CP-47,497 C8 homologue [cannabicyclohexanol], March 1, 2011), followed by the SDAPA (July 9, 2012) which permanently placed these initial five substances into Schedule I but also controlled a number of additional substances, manufacturers and users of synthetic cannabinoids then turned to new synthetic cannabinoids, namely UR-144, XLR11 and AKB48.

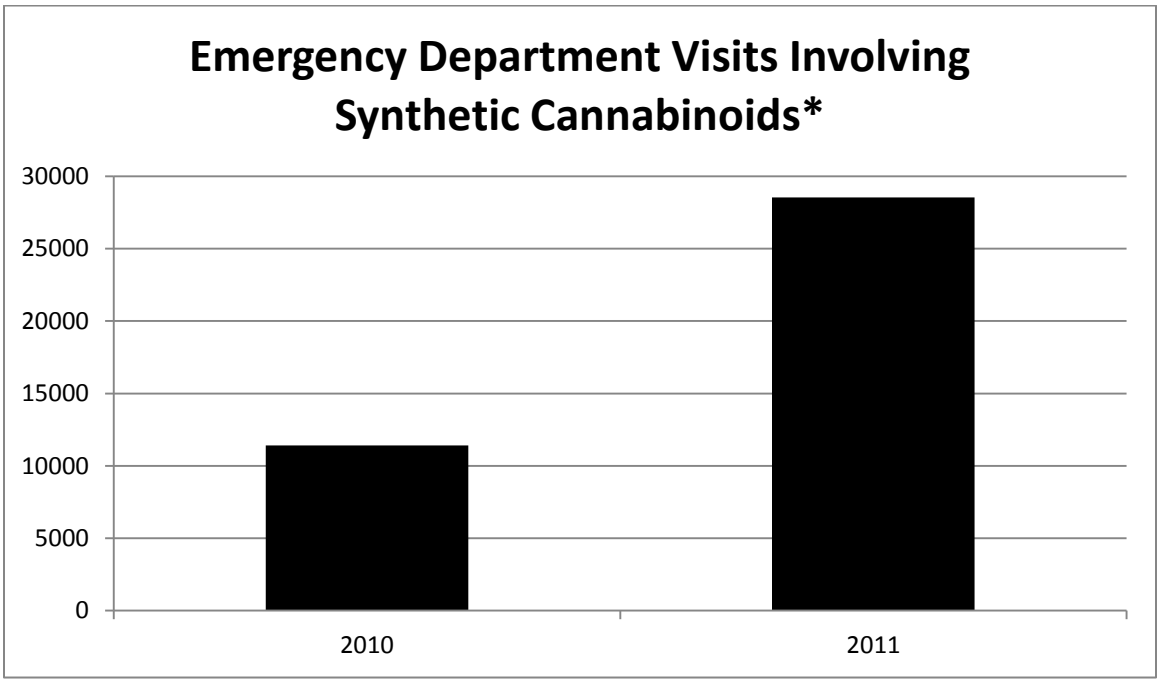

Figure 1. Emergency department visits involving synthetic cannabinoids (SAMHSA, 2013). Data were not collected prior to 2010.

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

Product analyses have yielded important information regarding these synthetic substances. Smoking mixtures sold in Russia have been analyzed and found to contain UR-144 along with other compounds, including JWH-018 (Sobolevsky et al., 2012). AKB48, UR-144 and XLR11 have also been identified in designer drugs currently being sold in Japan (Uchiyama, 2012a, Uchiyama et al., 2012b). The chronic abuse of products laced with synthetic cannabinoids has been linked to addiction and withdrawal (Vardakou et al., 2010).

Summary

The abuse of synthetic cannabinoids is characterized in the scientific literature and by law enforcement encounters with reported adverse health effects. Numerous

calls have been received by poison control centers regarding the abuse of products potentially laced with synthetic cannabinoids that have resulted in visits to emergency departments. Following the SDAPA in July of 2012, new generations of synthetic cannabinoids including UR-144, XLR11 and AKB48 increasingly replaced those cannabinoids that were placed into Schedule I of the CSA.

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 abuse of synthetic cannabinoids to both the individual abusers and other affected individuals since these substances were never intended for human use. Warnings regarding the dangers associated with abuse of synthetic cannabinoids and their products have been issued by numerous state public health departments and poison control centers and private organizations. Detailed product analyses describe variations in the amount and synthetic cannabinoid laced on the plant material even within samplings of the same product (Hudson et al., 2010). These unknowns present a significant risk or danger to the abusing individuals (Auwarter et al., 2009, Hudson et al., 2010). Wells and Ott stated concern regarding the possibility of serotonin syndrome related to synthetic cannabinoids of the indole structural class due to the similarity to serotonin (Wells and Ott, 2011). Some of the common clinical effects reported in emergency rooms in response to the abuse of synthetic cannabinoids include vomiting, anxiety, agitation, irritability, seizures, hallucinations, tachycardia, elevated blood pressure, and loss of consciousness (Harris and Brown, 2013; Hermanns-Clausen et al., 2012; Forrester et al., 2011; Cohen et al., 2012) (see reports from state health departments and poison centers including AAPCC, Appendix 1).

By sharing pharmacological similarities with the Schedule I substances (Δ^9-THC and JWH-018), synthetic cannabinoids pose a risk to the abuser (Weissman et al., 1982, Compton et al., 1992a, Wiley et al., 1998), and the chronic abuse of products laced with synthetic cannabinoids has been linked to addiction and withdrawal (Vardakou et al., 2010). Submissions to DEA laboratories from January 2012 through April 03, 2013 have documented over 150 distinct packaging examples containing mixtures of UR-144, XLR11 and/or AKB48. Similar products have been found to vary in the amount and type of synthetic cannabinoid laced on the plant material, which could by one explanation for the numerous emergency department admissions that have been connected to these substances (Vearrier and Osterhoudt, 2010, Schneir et al., 2011). In 2010, 11,406 emergency department visits involved a synthetic cannabinoid product (SAMHSA, 2012). In 2011, SAMHSA reported the number of emergency department visits involving a

synthetic cannabinoid product had increased 2.5 times to 28,531 (SAMHSA, 2013). Health warnings have been issued by numerous state public health departments and poison control centers describing adverse health effects associated with smoking (inhaling) these products including, agitation, vomiting, tachycardia, elevated blood pressure, seizures, hallucinations and non-responsiveness (Appendix 1).

Due to increasing trends in this newer generation of synthetic cannabinoids, UR-144 and XLR11 have been added to the toxicological panel (i.e. a list of synthetic cannabinoids commonly tested for) from two major laboratories. NMS Laboratories (Willow Grove, PA) re-analyzed 46 blood samples collected in July 2012. These samples had been positive for a synthetic drug compound, but were originally not tested for UR-144 or XLR11. Upon re-analysis, 27/46 (58%) were positive for UR-144 and 14/46 (30%) were positive for XLR11[8]. An additional 28 samples collected in December 2012 were analyzed using NMS Laboratories new scope which includes UR-144 and XLR11 testing. Results from these 28 samples demonstrated 8/28 (28%) positivity for UR-144 and 12/28 (44%) positivity for XLR11[9]. Redwood Laboratories (Santa Rosa, CA) has also recently added UR-144 and XLR11 to their toxicological panel. From January through June 2012, Redwood Laboratories reported between 6.5 – 9.7% positivity for synthetic cannabinoids, not including UR-144 or XLR11[10]. These levels diminished in the subsequent 6 months between July and December 2012, falling from 8.0 % in July 2012 to a low of 2.8% positivity in December 2012. Using a new panel, Redwood Laboratories re-analyzed 300 randomly chosen samples from December 2012, and found the positivity results climb to 16% (39/300 for UR-144 and/or XLR11 alone) for all synthetic cannabinoids tested when including UR-144 and XLR11 in the panel where tests without UR-144 and XLR11 showed only 2.8 % positivity (Table 2)[11]. These data suggest newer non-controlled synthetic cannabinoids are being abused, specifically UR-144 and XLR11. A third company, Premier Integrity Solutions (Russell Springs, KY), supplies the toxicological services for the state of Kentucky's drug court program. Data provided by the court coordinator for the state of Kentucky demonstrated that there were 310 drug tests for synthetic cannabinoids dating from July 1, 2012 through December 20, 2012. Of these 310 drug tests, 24 were positive for synthetic cannabinoids, with 19/24 showing positivity for UR-144 or one of its metabolite[12,13]. No testing for XLR11 was reported.

[8] Correspondence from NMS Laboratories to ODEC, DEA 12/31/2012
[9] Correspondence from NMS Laboratories to ODEC, DEA 12/20/2012
[10] Correspondence from Redwood Laboratories to ODEC, DEA 01/07/2013
[11] Correspondence from Redwood Laboratories to ODEC, DEA 01/07/2013
[12] Correspondence from Kentucky Court System to ODEC, DEA 12/20/2012
[13] Correspondence from Kentucky Court System to ODEC, DEA 12/21/2012)

Table 2. Synthetic Cannabinoid Testing by Redwood Laboratories

	Percent Positivity	
	Synthetic Cannabinoids[a] (Excluding UR-144/XLR11)	Synthetic Cannabinoids[b] (Including UR-144/XLR11)
December 2012	2.8 %	16 %

[a] 238/8118 total samples tested by Redwood Laboratories in December 2012

[b] 39/300 randomly selected samples by Redwood Laboratories from December 2012

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 THC-like substances. There is no accepted medical use of these substances in the United States.

In February 2013, the CDC published a report describing unexplained cases of acute kidney injury in 16 patients, all of whom had reported recent smoking of synthetic cannabinoids. Upon further investigation, it was determined that of the 16 patients, 7 of the subjects had smoked substances that were positive for XLR11 or its metabolite. Cases were reported from Wyoming (4 cases), Rhode Island (1 case), New York (2 cases), Oregon (6 cases), Kansas (1 case) and Oklahoma (2 cases) (Murphy et al., 2013).

According to a letter from Assistant Secretary of Health Howard Koh of the Department of Health and Human Services (dated March 14, 2013, see attached), the Food and Drug Administration has reported there are currently no approved drug applications and no investigational new drug applications for UR-144, XLR11 or AKB48. The Department of Health and Human Services has no objection as to DEA's plan to temporarily place UR-144, XLR11 and AKB48 into Schedule I of the CSA.

Conclusion of 3-Factor Analysis

After a careful review of the scientific literature, Factors 4, 5, and 6, NFLIS, STRIDE, and other law enforcement data and sources of information, it is evident that UR-144, XLR11, and AKB48 are trafficked and abused and pose a significant public health risk. These drugs have become popular among drug abusers due to their THC-like effects and pharmacological similarity to JWH-018.

DEA has considered the three criteria for placing a substance into Schedule I of the CSA (21 U.S.C. 812). The data available and reviewed for UR-144, XLR11, and AKB48 indicated that these substances, including their salts, isomers, and salts of isomers, pose an imminent hazard to public safety and health, have no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision.

References

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

Aung MM, Griffin G, Huffman JW, Wu M, Keel C, Yang B, Showalter VM, Abood ME, Martin BR (2000) Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB(1) and CB(2) receptor binding. Drug and alcohol dependence 60:133-140.

Auwarter V, Dresen S, Weinmann W, Muller M, Putz M, Ferreiros N (2009) 'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? Journal of mass spectrometry : JMS 44:832-837.

Choi T, Ma E (2010) Structural necessity of indole C5-O-substitution of seco-duocarmycin analogs for their cytotoxic activity. Molecules 15:7971-7984.

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

D'Ambra TE, Estep KG, Bell MR, Eissenstat MA, Josef KA, Ward SJ, Haycock DA, Baizman ER, Casiano FM, Beglin NC, et al. (1992) Conformationally restrained analogues of pravadoline: nanomolar potent, enantioselective, (aminoalkyl)indole agonists of the cannabinoid receptor. Journal of medicinal chemistry 35:124-135.

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

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

Elsken CS, Flores E, Forster MJ. (2013a). Time course (8-h) mouse locomotor activity test vs delta(9)-THC time course: UR-144. NIDA Contract N01DA-7-8872.

Elsken CS, Flores E, Forster MJ. (2013b). Time course (8-h) mouse locomotor activity test vs delta(9)-THC time course: XLR11. NIDA Contract N01DA-7-8872.

Elsken CS, Flores E, Forster MJ. (2013c). Time course (8-h) mouse locomotor activity test vs delta(9)-THC time course: AKB48. NIDA Contract N01DA-7-8872.

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

Frost JM, Dart MJ, Tietje KR, Garrison TR, Grayson GK, Daza AV, El-Kouhen OF, Miller LN, Li L, Yao BB, Hsieh GC, Pai M, Zhu CZ, Chandran P, Meyer MD (2008) Indol-3-yl-tetramethylcyclopropyl ketones: effects of indole ring substitution on CB2 cannabinoid receptor activity. Journal of medicinal chemistry 51:1904-1912.

Frost JM, Dart MJ, Tietje KR, Garrison TR, Grayson GK, Daza AV, El-Kouhen OF, Yao BB, Hsieh GC, Pai M, Zhu CZ, Chandran P, Meyer MD (2010) Indol-3-ylcycloalkyl ketones: effects of N1 substituted indole side chain variations on CB(2) cannabinoid receptor activity. Journal of medicinal chemistry 53:295-315.

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

Hassam M, Basson, A.E., Liotta, D.C., Morris, L., van Otterlo, W.A.L., Pelly, S.C. (2012) Novel cyclopropyl-indole derivatives as HIV non-nucleoside reverse transcriptase inhibitors. ACS Med Chem Lett 3:470-475.

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

Huffman JW, Dong, D., Martin, B.R., Compton, D.R. (1994) Design, synthesis and pharmacology of cannabimimetic indoles. Bioorg Med Chem Letters 4:563-566.

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

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

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

Makriyannis A and Liu, Q. (2003) Heteroindanes: A new class of potent cannabimimetic ligands *(patent).* WO 03/035005 A2.

Milbank JB, Tercel M, Atwell GJ, Wilson WR, Hogg A, Denny WA (1999) Synthesis of 1-substituted 3-(chloromethyl)-6-aminoindoline (6-amino-seco-CI) DNA minor groove alkylating agents and structure-activity relationships for their cytotoxicity. Journal of medicinal chemistry 42:649-658.

Muller H, Sperling W, Kohrmann M, Huttner HB, Kornhuber J, Maler JM (2010) The synthetic cannabinoid Spice as a trigger for an acute exacerbation of cannabis-induced recurrent psychotic episodes. Schizophrenia research 118:309-310.

Pace JM, Tietje, K., Dart, M.J., Meyer, M.D. (2006) 3- Cycloalkylcarbonyl indoles as cannabinoid receptor ligands *(patent)*. WO 2006/069196 A1.

Perkin Elmer (2013a). Cannabinoid, CB1 (h) Agonist Cellular/Functional Assay. TDP# UR-144. NIDA Contract N01DA-8-8877.

Perkin Elmer (2013b). Cannabinoid, CB1 (h) Agonist Cellular/Functional Assay. TDP# XLR11. NIDA Contract N01DA-8-8877.

Perkin Elmer (2013c). Cannabinoid, CB1 (h) Testing Profile and IC50/Ki Determination. TDP# AKB48. NIDA Contract N01DA-8-8877.

Perkin Elmer (2013d). Cannabinoid, CB1 (h) Agonist Cellular/Functional Assay. TDP# AKB48. NIDA Contract N01DA-8-8877.

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

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

SAMHSA (2013). Drug Abuse Warning Network, 2011: Selected Tables of National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: Center for Behavioral Health Statistics and Quality.

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

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

Sharma SK, Jia G, Lown JW (2001) Novel cyclopropylindole conjugates and dimers: synthesis and anti-cancer evaluation. Current medicinal chemistry Anti-cancer agents 1:27-45.

Sobolevsky T, Prasolov I, Rodchenkov G (2012) Detection of urinary metabolites of AM-2201 and UR-144, two novel synthetic cannabinoids. Drug testing and analysis.

Teske J, Weller JP, Fieguth A, Rothamel T, Schulz Y, Troger HD (2010) Sensitive and rapid quantification of the cannabinoid receptor agonist naphthalen-1-yl-(1-pentylindol-3-yl)methanone (JWH-018) in human serum by liquid chromatography-tandem mass spectrometry. Journal of chromatography B, Analytical technologies in the biomedical and life sciences 878:2659-2663.

Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y (2012b) URB-754: A new class of designer drug and 12 synthetic cannabinoids detected in illegal products. Forensic science international.

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

Uchiyama N, Kikura-Hanajiri R, Matsumoto N, Huang ZL, Goda Y, Urade Y (2012c) Effects of synthetic cannabinoids on electroencephalogram power spectra in rats. Forensic science international 215:179-183.

Uchiyama N, Kikura-Hanajiri R, Ogata J, Goda Y (2010) Chemical analysis of synthetic cannabinoids as designer drugs in herbal products. Forensic science international 198:31-38.

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

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

Wang Y, Gupta R, Huang L, Luo W, Lown JW (1996) Design, synthesis, cytotoxic properties and preliminary DNA sequencing evaluation of CPI--N-methylpyrrole hybrids. Enhancing effect of a trans double bond linker and role of the terminal amide functionality on cytotoxic potency. Anti-cancer drug design 11:15-34.

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

Wells DL, Ott CA (2011) The "new" marijuana. The Annals of pharmacotherapy 45:414-417.

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

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

Appendix 1

Public Health

1. The Substance Abuse and Mental Health Services Administration (SAMHSA) reported that in 2010, and estimated 11,406 emergency department visits involved a synthetic cannabinoid product.
2. Monitoring the Future study results for 2012 (released 12/19/2012) state that for the second year of reporting, use of synthetic marijuana amongst 12^{th} graders held level at 11.3%. Study authors stated that while a leveling was encouraging, the high prevalence rate despite federal and state efforts to reduce its use was troublesome.
3. State of Kentucky Drug Court reported that out of 24 positive tests for synthetic cannabinoids from September 2012 through December 2012, 19 of these tests were positive for UR-144. (XLR11 and AKB48 were not tested in these samples)
4. NMS laboratories re-evaluated 50 blood samples originally tested in July 2012 that were negative for synthetic cannabinoids. After further screening in December 2012 for UR-144 and XLR11, 27/50 samples tested positive for UR-144 and 14/50 samples tested positive for XLR11.
5. NMS laboratories evaluated 28 new blood samples in December 2012 using a new platform that included testing for UR-144 and XLR11. 8/29 samples tested positive for UR-144 and 12/28 samples tested positive for XLR11.
6. Redwood laboratories used a newly validated method to re-test samples in December 2012 for UR-144 and XLR11. Of the 300 randomly chosen samples that were originally negative for synthetic cannabinoids, 39/300 were found to contain metabolites of either UR-144 and/or XLR11.
7. DEA laboratories have reported over 144 individual spice products that tested positive for UR-144, XLR11 and/or AKB48 ranging from November 2012 through January 2013.

Poison Control Centers

1. **March 24 AAPCC Press Release.** As of March 24, 2010, 112 calls had been received since 2009 regarding synthetic cannabinoids and associated products, including 59 calls since March 1, 2010, according to NPDS.
2. **July 23, 2010 AAPCC Press Release.** As of July 23, 2010, 761 calls had been received regarding synthetic cannabinoids and associated products according to NPDS.
3. **August 20, 2010 AAPCC Press Release.** As of August 20, 2010, 1,057 calls had been received regarding synthetic cannabinoids and associated products according to NPDS.

4. **September 27, 2010 AAPCC Press Release.** As of September 27, 2010, 1,503 calls had been received regarding synthetic cannabinoids and associated products according to NPDS.
5. **November 3, 2010 AAPCC Press Release.** As of November 3, 2010, 1,966 calls have been received by poison centers regarding products purported to contain synthetic cannabinoids according to the National Poison Data System (NPDS). Calls have been received in 48 states and the District of Columbia.
6. **November 22, 2010 AAPCC Press Release**. As of November 22, 2010, poison centers have reported 2,304 calls regarding products purported to contain synthetic cannabinoids according to the National Poison Data System (NPDS). Poison centers have received calls in 49 states and the District of Columbia.
7. **December 21, 2010 AAPCC Press Release.** As of December 21, 2010, U.S. poison centers have reported receiving more than 2,500 calls this year alone. As of December 21, 2010, poison centers have reported 2,752 calls about the products according to the National Poison Data System (NPDS).
8. **January 18, 2011 AAPCC Press Release.** As of January 18, 2011, U.S. poison centers have received more than 3,000 calls regarding products purported to contain synthetic cannabinoids. In 2010, poison centers reported 2,867 calls. As of January 18, 2011, U.S. poison centers have reported 217 calls for 2011.
9. **February 3, 2011, AAPCC Press Release.** As of February 3, 2011, U.S. poison centers have reported 385 calls for 2011.
10. **February 10, 2011, AAPCC Press Release.** Synthetic marijuana products have spurred more than 3,000 calls to U.S. poison centers since 2010.
11. **February 24, 2011, AAPCC Press Release.** As of February 24, 2011, U.S. poison centers have reported 706 calls for 2011. The total number of calls since 2010 is more than 3,500 calls.
12. **April 20, 2011, AAPCC Press Release.** Synthetic marijuana products have spurred more than 4,500 calls to U.S. poison control centers since 2010.
13. **July 11, 2012, AAPCC Press Release.** In 2010, poison centers nationwide responded to about 3,200 calls related to synthetic marijuana and bath salts. In 2011, the number jumped to more than 13,000. Sixty percent of these cases involved patients 25 and younger.
14. **November 28, 2011, AAPCC Press Release.** Poison center data provides vital information leading to DEA ban of synthetic drugs.
15. **February 16, 2012, AAPCC Press Release.** American Association of Poison Control Centers joins the Office of National Drug Control Policy Working Group in address the dangers if synthetic drugs.

16. **May 31, 2012, AAPCC Press Release.** The AAPCC commends the U.S. Senate for passing a ban of synthetic drugs in SB 3187 and call on the U.S. House of Representatives to include the language in the final version of the bill.
17. **July 11, 2012, AAPCC Press Release.** AAPCC comment the nation's policy makers on passage into the law the Synthetic Drug Abuse Prevention Act of 2012.
18. **From January 1, 2012 through December 31, 2012**, poison centers nationwide have received 5,200 calls regarding exposure to synthetic cannabinoids.

Relevant Positions/Statements by Organizations

A. National Drug Court Institute, Drug Court Practitioner Fact Sheet, *Spice, K2 and the Problem of Synthetic Cannabinoids*, October 2010, vol. 5, no. 1. (www.ndci.org)
B. MetroKids, *'Spice' Health Warning Issued*, April 2010 (www.metrokids.com)
C. Indiana Prevention Resource Center, Indiana University Bloomington, *K2/Spice: A Fake Drug Carrying a Real Potential for Harm*, undated, (www.drugs.indiana.edu)
D. Prevention First, *Fake Marijuana Called Spice or K2 Can Cause Serious Harm to Teens*, April 13, 2010 (www.prevention.org)
E. Saint Louis University, *SLU Toxicologist Warning to Parents: Look for Signs of K2*, March 3, 2010 (www.slu.edu/x35328.xml)
F. Community of Anti-Drug Coalitions of America, *Researchers Warn About Dangers of Synthetic Marijuana*, March 18, 2010 (www.cadca.org)

NFLIS Reports (as of April 03, 2013)*:

	JAN - MAR 2010	OCT - DEC 2011	JAN - MAR 2012	APR - JUN 2012	JUL - SEP 2012	OCT - DEC 2012	JAN – MAR 2013	TOTAL
AKB48	-	47	94	167	141	63	13	525
UR-144	1	-	360	1,687	2,397	788	123	5,356
XLR11	-	-	83	1,338	3,037	2,772	845	8,075

* No reports identified in NFLIS regarding UR-144, XLR11 or AKB48 prior to January 1, 2010

STRIDE Records (January 1, 2009 through April 03, 2013)*:

	CASES	RECORDS
AKB48	40	112
UR-144	179	1,510
XLR11	186	1,194

* No reports identified in STRIDE regarding UR-144, XLR11 or AKB48 prior to January 1, 2009

DEA Sample Laboratory Results

Date	Label	Flavor/ Characteristic	Confirmed Substance	Lab	Notes
3/29/2013	Bizarro; Zensence		XLR-11	Northeast	Black packet, purple yellow reversed superman, 1.5 g
3/29/2013	Orgazmo; Zensence		XLR-11	Northeast	Red circle, yellow lightning bolt, 1.5g
3/28/2013	Scooby Snax		XLR-11, 5-Cl-UR-144	Southwest	10g packet, Tie-dyed front purple/yellow, Scooby doo on front
3/28/2013	Green Giant		XLR-11	Southwest	3g, green cartoon on front, orange hair, green packet
3/27/2013	Scooby Snax		XLR-11	Southwest	4g packet, Tie-dyed front, Scooby doo on front
3/27/2013	Kush 10X	Kryptonite	XLR-11	Southwest	3g, Green lettering on front
3/27/2013	WTF		XLR-11	Southwest	Fidel Castro on toilet, no toilet paper
3/27/2013	Diablo		XLR-11	Southwest	3g packet, skull on fire
3/20/2013	Smokin Dragon Potpourri	Strawberry	XLR-11	Southwest	Clear plastic vial with green cap, purple/pink dragon on front
3/20/2013	Smokin	Pomegranate	XLR-11, UR-	Southwest	Clear plastic vial

	Dragon Potpourri		144		with green cap, purple/pink dragon on front
3/20/2013	Smokin Dragon Potpourri	Strawberry	XLR-11	Southwest	Clear plastic vial with green cap, purple/pink dragon on front
3/20/2013	Mad Hatter	Blueberry	XLR-11	Northeast	3g packet, blue background, Madd Hatter tipping hat
3/15/2013	Puff	Hypnotic	XLR-11, UR-144	Southwest	Clear plastic vial with black cap, dragon on front
3/15/2013	Smokin Dragon Potpourri	Hypnotic	XLR-11, UR-144	Southwest	Clear plastic vial with red cap, purple/pink dragon on front
3/15/2013	Smokin Dragon Potpourri	Pomegranate	XLR-11, UR-144	Southwest	Clear plastic vial with purple cap, purple/pink dragon on front
3/15/2013	Smokin Dragon Potpourri	Blueberry	XLR-11, UR-144	Southwest	Clear plastic vial with red cap, purple/pink dragon on front
3/8/2013	Diablo		XLR-11, 5-Cl-UR-144	Southwest	3g packet, skull on fire
3/6/2013	G-20		XLR-11	Southwest	4g, G-20 on front, black and red packet, Mr. Happy
3/6/2013	G-20		XLR-11	Southwest	G-20 on front, black and white writing, Mr. Happy
3/6/2013	Mr. Happy	Blueberry	XLR-11	Southwest	Smiley face in yellow, green, red, purple and yellow
3/6/2013	Mr. Happy		XLR-11	Southwest	Smiley face, black and white
3/6/2013	Diablo		XLR-11	Southwest	3g packet, skull on fire
3/6/2013	Diablo		XLR-11, UR-144	Southwest	3g packet, skull on fire
3/6/2013	Bizarro;	Lime	XLR-11	Northeast	Black packet,

	Zensence				purple yellow reversed superman, 1.5 g
3/5/2013	Everest	12 diff. flavors	XLR-11	Northeast	3.5 g, gold packet, blue mountains, The highest peak on earth
3/5/2013	Liberty Herbal Incense	Sweet Domination	UR-144	Northeast	3g, silver packet, liberty bell on front
3/5/2013	Smokin Dragon Potpourri	4 flavors, 3 strengths	XLR-11, 5-Cl-UR-144	Northeast	Clear plastic vial with red/green/tan cap, purple/pink dragon on front
3/4/2013	Darkness	Purple Haze	XLR-11, UR-144, 5-Cl-UR-144	Northeast	5g, face in shadow, black, packet
3/4/2013	Darkness	Purple Haze	XLR-11, UR-144	Northeast	5g, face in shadow, black, packet
3/4/2013	Mystic	Forbidden Fruit	XLR-11	Northeast	6g, Medusa on front
3/4/2013	WTF		XLR-11	Northeast	Fidel Castro on toilet, no toilet paper
3/4/2013	Down2Earth	Purple Chronic	XLR-11, UR-144, 5-Cl-UR-144	Northeast	10g, multi-color, octopus standing on green mushrooms, cartoon
3/4/2013	AK-47	Kush	XLR-11	Northeast	3g packet, red black, silhouette woman holding rifle
2/26/2013	Bizarro; Zensence	Cherry	XLR-11	Northeast	Black packet, purple yellow reversed superman, 1.5 g
2/26/2013	Bizarro; Zensence	Cherry	XLR-11	Northeast	Black packet, purple yellow reversed superman, 1.5 g

2/26/2013	Bizarro; Zensence	Cherry	XLR-11	Northeast	Black packet, purple yellow reversed superman, 1.5 g
2/26/2013	Bizarro; Zensence	Lime	XLR-11	Northeast	Black packet, purple yellow reversed superman, 1.5 g
2/25/2013	Syn Swag		XLR-11	Western	Business man devil, wings, orange, blue suit black packet
2/25/2013	WTF		XLR-11	Western	Fidel Castro on toilet, no toilet paper
2/25/2013	Syn Smooth		XLR-11	Western	Purple black packet, devil on front, thumbs up
2/11/2013	Diablo		XLR-11, UR-144	Southwest	3g packet, skull on fire
2/7/2013	The Original Cloud Nine		XLR11	Southwest	1g packet, light blue, smiling cloud on front
2/7/2013	Diablo		XLR11, UR-144	Southwest	3g packet, skull on fire
2/7/2013	Smokin Dragon Potpourri	Blueberry	XLR11	Southwest	Clear plastic vial with RED cap, purple/pink dragon on front
1/18/2013	Kaptain Kush	Strawberry	XLR11, 5-Cl-UR-144	Southwest	Clear plastic vial with red cap, skeleton pirate with K on hat
1/18/2013	Kaptain Kush	Kush	XLR11, 5-Cl-UR-144	Southwest	Clear plastic vial with green cap, skeleton pirate with K on hat
1/18/2013	Kaptain Kush	Hypnotic	XLR11, 5-Cl-UR-144	Southwest	Clear plastic vial with red cap, skeleton pirate with K on hat
1/17/2013	Ultra Zombie Matter Halo	Dusk	XLR11	Western	Small glass or plastic jar/container
1/14/2013	Legal Devil		XLR11	Southwest	Clear plastic vial

	Potpourri				with red cap, X, picture of man/devil on front
1/14/2013	Hi 5		XLR11	Southwest	Clear plastic vial, tan cap, green looking shamrock on front
1/12/2013	Handy		XLR11	Southwest	Clear plastic vial with red cap, blue handicap daigram on front
1/12/2013	Hi5 Potpourri Hi 5		XLR11	Southwest	7g clear plastic vial, tan cap, green looking shamrock on front
1/12/2013	Fly'n High	Kush	XLR11	Southwest	Clear plastic vial with black cap, Bob Marley on front in green
1/12/2013	Fly'n High	Strawberry	XLR11	Southwest	Clear plastic vial with red cap, Bob Marley on front in red
1/12/2013	Fly'n High	Blueberry	XLR11	Southwest	Clear plastic vial with blue cap, Bob Marley on front in blue
1/12/2013	Kaptain Kush	Blueberry	XLR11	Southwest	Clear plastic vial with red cap, skeleton pirate with K on hat
1/12/2013	Smokin Dragon Potpourri	Cherry	XLR11, UR-144	Southwest	Clear plastic vial with green cap, purple/pink dragon on front
1/11/2013	Luscious Aroma	Grape	UR-144	Northeast	Small clear glass or plastic jar/container
1/11/2013	Luscious Aroma	Strawberry	UR-144	Northeast	Small clear glass or plastic jar/container
1/11/2013	Ultra Zombie Matter Halo		XLR11	Northeast	Small glass or plastic

					jar/container
1/11/2013	Madd Hatter		XLR11, UR-144	Southwest	3g packet, Madd Hatter with Aces coming from sleeve on front
1/11/2013	Madd Hatter		UR-144	Southwest	3g packet, Madd Hatter with Aces coming from sleeve on front
1/11/2013	Joker		XLR11	Southwest	4g black packet, Joker on front, face is silver glitter, red lips.
1/11/2013	Scooby Snax		XLR11	Southwest	4g packet, Tie-dyed front, Scooby doo on front
1/10/2013	Sin City	Watermelon	XLR11	Southwest	2g clear vial, Red cap, green plant material
1/10/2013			XLR11	Southwest	1kg silver packet, no labeling
1/9/2013	M G		XLR11	Mid-Atlantic	10g, Snow white dwarf on front, green package Mr. Nice Guy
1/8/2013	Sky Bomb		XLR11	Northeast	1.25 grams, small glass or plastic jar/container
1/8/2013	Sky Pilot		XLR11	Northeast	Small packet, fighter pilot with mask on front
1/8/2013	Blue Kush	Ltd Edition	XLR11	Northeast	Small packet, blue lettering with crown on top of SH
1/8/2013	Black Venom		XLR11	Northeast	Black packet, eyes on front
1/8/2013	Ultra Zombie Matter Halo	Dusk	XLR11	Northeast	Small glass or plastic jar/container

12/14/2012	Ultra Zombie Matter Halo	Twilight	XLR11	Western	Small glass or plastic jar/container
12/14/2012	Ultra Zombie Matter Halo	Midnight	XLR11	Western	Small glass or plastic jar/container
12/13/2012	Mary & Jane		XLR11, UR-144	Southwest	Black packet, two naked females on front (blonde, brunette kneeling)
12/13/2012	Miami Spice		XLR11, UR-144	Southwest	Black packet, picture of Miam Blvd. on front
12/13/2012	Screamin Demon		XLR11, UR-144	Southwest	Black packet, skull in flames on front
12/13/2012	Shockwave		XLR11, UR-144	Southwest	Black packet, screaming man with headphones
12/7/2012	Hammer Head		XLR11	Northeast	Black packet, no weight, white skull with stars on forehead
12/7/2012	AK-47		XLR11, UR-144	Northeast	3g, silver and yellow, picture of AK-47 on front
12/7/2012	AK-47		XLR11	Northeast	3g, silver and red, picture of AK-47 on front
12/7/2012	Platinum, Caution		XLR11, UR-144	Northeast	3g, packet has glitter, silver background, biohazard symbol
11/30/2012	M G	Blueberry	XLR11	South Central	12g, Snow white dwarf on front, green packate, Mr. Nice Guy
11/30/2012	You Only Live Once		XLR11, UR-144	Southwest	3g black packet, red writing
11/30/2012	Demon		XLR11, UR-144	Southwest	Orange packet, red word

					"demon" behind
11/30/2012	Dank		XLR11, UR-144	Southwest	Small plastic vial, Mr. Nice guy smiley with XX eyes
11/20/2012	Aloha…get Lei'd	Blueberry	XLR11, UR-144	Mid-Atlantic	Small glass or plastic jar/container
11/20/2012	Ultra Zombie Matter Halo		XLR11	Western	Small glass or plastic jar/container
11/20/2012	Ultra Zombie Matter Halo	Twilight	XLR11	Western	Small glass or plastic jar/container
11/20/2012	Ultra Zombie Matter Halo	After Dark	XLR11	Western	Small glass or plastic jar/container
11/16/2012	NOLA Diamond Potourri	Hypnotic	XLR11	Southwest	3g packets
11/16/2012			XLR11	Southwest	White and black bricks of substance
11/15/2012	Relaxinol		XLR11	Southwest	Mr. Nice Guy, rabbit holding a pocket watch by mushrooms
10/31/2012			AKB48	Southwest	
10/31/2012			XLR11	Southwest	XLR11 identified in 6/14 substances tested
10/26/2012			AKB48	Southwest	
10/25/2012	Sonic Zero; Zensence	Blueberry	XLR11	Southwest	1.5g long glass vial
10/25/2012	Bizarro; Zensence	Strawberry	XLR11	Mid-Atlantic	1.5g packet, reverse superman in purple and yellow
10/22/2012	Avalanche; Zensence	Pineapple	XLR11	Western	1.5g packet, snowcapped mountains, light blue
10/22/2012	Neutronium; Zensence		XLR11, UR-144	Western	3.5g packet, black,

					atom/electrons
10/22/2012	Bizarro; Zensence	Cherry	XLR11	Western	1.5g packet, reverse superman in purple and yellow
10/22/2012	Bizarro; Zensence	Blueberry	XLR11	Western	1.5g packet, reverse superman in purple and yellow
10/10/2012	Fly'n High	Blueberry	XLR11	Henderson PD Nevada	2.09, plastic tube, picture of Bob Marley
10/10/2012	Lava Extra Strength	Strawberry	XLR11, UR-144	Mid-Atlantic	Red/black packet, volcano and lava
10/10/2012	Pure Sin		XLR11, UR-144	Mid-Atlantic	3g packet, 3 skulls on front, red barbed wire on reverse
10/9/2012			XLR11, UR-144	Southwest	Unlabeled small clear glass jar, black cap
10/4/2012	K4 Max		UR-144	Western	3g, clear packet, compass on front
10/3/2012	Clown Loyal	Original	XLR11	Western	2g, black plastic container
10/3/2012	Mad Monkey	Strawberry	XLR11, UR-144	Southwest	5g, cartoon monkey on front, reverse states "Its LEGAL"
10/3/2012	7H	4:20	XLR11, UR-144	Southwest	7H combination in multiple circles on label, LEGAL
10/3/2012	Zombie Life		XLR11, UR-144	Southwest	3g packet, tombstone on front, labeled K and H on top
9/19/2012	Purple Diesel		XLR11, UR-144	Southwest	3g packet, psycadelic front, glitter, starburst
9/19/2012	Sour Diesel	Original	XLR11	Southwest	Clear small

					plastic bag
9/19/2012	Diablo	Original	XLR11, UR-144	Southwest	3g packet, skull on fire
9/17/2012	Diablo		XLR11, UR-144	Southwest	3g packet, skull on fire
9/17/2012	Wanted		XLR11, UR-144	Southwest	3g packet, Wanted poster, skull and crossbones
9/12/2012			XLR11, UR-144	Southwest	
9/12/2012			XLR11	Southwest	
9/12/2012			XLR11, UR-144	Southwest	
9/10/2012	Sonic Boom		XLR11, UR-144	Southwest	2g/4g, Wicked LLC, red smoke rising
9/10/2012	Supernova		XLR11	Western	Small plastic container, blue star in background
9/10/2012	Zombie Matter Halo	Acid Rain	XLR11	Western	1g, Small plastic container, biohazard symbol in black/yellow
9/10/2012	Zombie Matter Halo	Midnight	XLR11	Western	1g, Small plastic container, biohazard symbol in black/yellow
9/5/2012	Tiger Shark		XLR11, UR-144	Southwest	4g, picture of tiger shark swimming
9/5/2012	New King Kong		XLR11	Southwest	3g, picture of screaming gorilla
9/5/2012	Atomic		XLR11, UR-144	Southwest	4g, picture of nuclear explosion
9/5/2012	New King Kong		XLR11, UR-144	Southwest	3g, picture of screaming gorilla
9/4/2012	9mm XXX	Blueberry	XLR11	Southwest	2g, plastic vial, clear
9/4/2012	Purple Diesel	Hydro	XLR11, UR-144	Southwest	3g packet, psycadelic

					front, glitter, starburst
9/4/2012	7H	4:20	XLR11, UR-144	Southwest	7H combination in multiple circles on label, LEGAL
8/31/2012	Mr. Happy	Original	XLR11, UR-144	Southwest	Smiley face in yellow, green, red, purple and yellow
8/31/2012	7-g Smoking Rasta		UR-144	Southwest	Cannabis leaves around small round vial, metal cap
8/30/2012			XLR11, UR-144	Southwest	Black packet, no labeling
8/30/2012	Bloody Mary Halo		XLR11	Western	Kneeling woman, halo on head, stone statue
8/29/2012	Zombie Matter Halo	Blackout	XLR11	Western	1g, Small plastic container, biohazard symbol in black/yellow
8/29/2012	$25K		UR-144	Mid-Atlantic	2g white packet, green spiral of smoke
8/29/2012	$25K		UR-144	Mid-Atlantic	5g silver packet, green spiral of smoke
8/27/2012	Anarchy		UR-144	Western	Small glass jar, black lid, gray background
8/23/2012	Scooby Snax	Second Generation	XLR11, UR-144	Southwest	10g packet with pink background, glittered Scooby-Doo
8/23/2012	Mad Monkey		XLR11, UR-144	Southwest	5g, cartoon monkey on front, reverse states "Its LEGAL"
8/21/2012	White Widow	Da Brand	XLR11, UR-144	Southwest	6cm clear plastic vial, black widow

					spider on front
8/21/2012	Hayze Hawaiian		XLR11	Western	1.5g packet with volcano on front, white background
8/21/2012	Super Stank	Fragrance of Skunk	XLR11	Western	2g packet with brown skunk on front, black background
8/17/2012	Knockout	Original	XLR11	Southwest	Small clear plastic bag
8/17/2012	Purple Diesel	420	XLR11	Southwest	3g packet, psycadelic front, glitter, starburst
8/13/2012	Kosmic Kush		XLR11	Southwest	2.5g packet, planet system in brown and black
8/13/2012	New King Kong		XLR11	Southwest	3g, picture of screaming gorilla
8/13/2012	Botanical Potpouri	Hydro; 7H	XLR11	Southwest	Skulls with horns, 7H and red/yellow flames
7/27/2012	Sonic Boom		UR-144	Northeast	2g/4g, Wicked LLC, red smoke rising
7/23/2012	Hysteria Black	Mr. Bubble	XLR11, UR-144	Western	5g, black packet, red lines on back
7/23/2012	Hysteria Black	Joocy Fruit	XLR11, UR-144	Western	5g, black packet, red lines on back
7/23/2012	Black Sabbath	Groovy Grape	XLR11	Western	
7/20/2012	Hayze Hawaiian Ultra		UR-144	Western	1.5g packet with volcano on front, white background
7/19/2012	Joker		XLR11, UR-144	Southeast	4g black packet, Joker face from Batman
7/19/2012	Mind Trip		XLR11, UR-144	Southeast	4g packet, skull with glitter around

7/19/2012	Out World		UR-144	Southeast	4g packet, upside down city, XXX sun, moon, cloud
7/13/2012	Express Barely Legal		XLR11	Southeast	3g red packet, cartoon young girl, roller-skates, food tray
7/13/2012	Barely Legal High Octane	Apple	UR-144	Southeast	1g packet, checkered flag, young girl with gas pump
7/13/2012	Barely In		XLR11	Southeast	1g red packet, crying schoolgirl, Mr. Nice guy behind, chalkboard
7/13/2012	Mad Hatter/Cloud 9	Second Generation	XLR11, UR-144	Southeast	10g, cartoon of mad hatter
7/13/2012	Kick Ass		UR-144	Southeast	3g, ninja on front
7/11/2012			XLR11, UR-144	Henderson PD Nevada	1.52g
7/11/2012			UR-144	Henderson PD Nevada	0.14g
7/5/2012	Relaxinol LE		UR-144	Southeast	1g, Mr. Nice guy, black packet
7/3/2012	Mr. Nice Guy	Strawberry	XLR11, UR-144	Southeast	1g, red strawberry
6/25/2012	Vesuvius	South Pacific	XLR11	Western	3g packet, clouds over mountain
6/25/2012	Vesuvius	Sex	XLR11	Western	3g packet, clouds over mountain
6/25/2012	Vesuvius	Sexy	XLR11	Western	3g packet, pink smoke strands, white background
6/18/2012	Hayze Hawaiian		XLR11	Western	1.5g packet with volcano on

	Ultra				front, white background
6/5/2012	Dead Man Walking		UR-144	Northeast	Clear vial, black cap, white label with skeleton
6/5/2012	Sam Pie		UR-144	Northeast	Clear vial, black cap, black label WARNING not for hum. Consump.
6/5/2012	Fire Extreme		UR-144	Northeast	Clear vial, black cap, black label
6/1/2012	Vesuvius	Sky	XLR11	Western	3g packet, clouds over mountain
6/1/2012	Vesuvius	Eruption	XLR11	Western	3g packet, clouds over mountain
6/1/2012	Vesuvius	Huckle Berry	XLR11	Western	1g, Small white plastic container
6/1/2012	Vesuvius	South Pacific	XLR11	Western	1g, Small white plastic container
6/1/2012	Vesuvius	Carnival	XLR11	Western	1g, Small white plastic container
5/22/2012	Green Cobra	Hypnotic	XLR11	Northeast	1.5g packet, cartoon of cobra snake
5/22/2012	Super Kush	Honeysuckle	XLR11	Northeast	1.5g packet, black background
4/27/2012	Black Mamba	DP	UR-144	Northeast	Clear vial, black cap, black label
4/27/2012	Mr. Spice Green		UR-144	Northeast	Clear vial, black cap, green label with cartoon man
4/27/2012	Magic Man		UR-144	Northeast	1.5g clear packet, white label, red skeleton, green star
4/18/2012	Mary Janes	Private Reserve	UR-144	Southwest	Clear vials, gold label or print on vial, woman

					side profile various colors (gold, blue, purple, pink, red writing on gold label)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the Assistant Secretary for Health
Washington, D.C. 20201

MAR 14 2013

Mr. Thomas M. Harrigan
Deputy Administrator
Drug Enforcement Administration
U.S. Department of Justice
8701 Morissette Drive
Springfield, VA 22152

Dear Mr. Harrigan:

Thank you for your recent letter notifying me of your intention to temporarily place 1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole [street name: UR-144], 1-(5-fluoro-pentyl)-3-(2,2,3,3-tetramethylcyclopropoyl)indole [street names: 5-fluoro-UR-144 and XLR-11], and *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide [street names: APINACA and AKB-48] into Schedule I of the Controlled Substances Act (CSA)

I asked the Food and Drug Administration to review its files, and the agency has advised me that there are currently no approved new drug applications and no investigational new drug applications in effect for any of these substances. Therefore, the Department of Health and Human Services has no objection regarding your plans to temporarily place UR-144, 5-fluoro-UR-144, XLR-11, APINACA, and AKB-48 into Schedule I of the CSA.

Sincerely yours,

Howard K. Koh, M.D., M.P.H.
Assistant Secretary for Health

U.S. Public Health Service

Jordan Trecki, Ph.D.

Jordan.Trecki@usdoj.gov

Pharmacologist, Drug Enforcement Administration (DEA)

EDUCATION

Doctorate of Philosophy (Ph.D.) in Pharmacology 2009
Temple University School of Medicine
Philadelphia, PA

Master of Science (M.S.) in Biotechnology 2004
Georgetown University
Washington, DC

Bachelor of Science (B.S.) in Biochemistry 2001
Duquesne University
Pittsburgh, PA

PROFESSIONAL EXPERIENCE

Pharmacologist
Drug Enforcement Administration (DEA)
Washington, DC
2012-present

Adjunct Professor, Environmental Management
University of Maryland University College
Adelphia, MD
2012-present

Neuropharmacologist/Neurotoxicologist/Chemical Manager
Environmental Protection Agency (EPA)
Washington, DC
2010-2012

Post-Doctoral Research Fellow, Neurodegenerative Diseases and Traumatic Brain Injury
Georgetown University Medical Center, Department of Neuroscience
Washington, DC
2009-2010

Adjunct Professor, Cellular Pharmacology and General Biology
Temple University School of Medicine
Philadelphia, PA
2006-2009

Jordan Trecki, PhD

Pharmacology Doctoral Candidate. Behavioral Pharmacology
Temple University School of Medicine, Department of Pharmacology
Philadelphia, PA
2004-2009

Oak Ridge Institute for Science and Education (ORISE) Fellow, Molecular Virology
Center for Biologics Evaluation & Research (CBER), Food and Drug Administration (FDA)
Bethesda, MD
2004

Clinical Laboratory Manager, Department of Allergy, Immunology and Infectious Disease
Children's Hospital of Pittsburgh/Allegheny General Hospital
Pittsburgh, PA
2001-2003

Laboratory Technician
Department of Biology, Duquesne University
Pittsburgh, PA
1998-1999

RESEARCH FUNDING AWARDED

1F31DA024516-01A1 - SDF-1a/CXCL12 Potentiates the Behavioral Effects of Cocaine in Rats
2008 – 2009

PEER-REVIEWED PUBLICATIONS

1. Trecki J, Szabo DT. Statistical significance versus biological relevance: A case study in behavioral testing. In preparation.

2. Powers CM, Gillespie PA, Bale A, Kraft A, Makris S, **Trecki J**, Cowden J, Hotchkiss A. Developmental Neurotoxicity of Engineered Nanomaterials: Identifying Research Needs to Support Risk Assessment. Submitted to Journal of Toxicological Sciences, January 2013.

3. Béraud D, Hathaway H, **Trecki J**, Chasovskikh S, Federoff J, Shimoji M, Mhyre T, Maguire-Zeiss KA. The Parkinson's disease protein α-synuclein induces an Nrf2-mediated antioxidant response. J Neuroimmune Pharmacol. 2012 Oct 10.

4. Trecki J, Brailoiu GC, Unterwald EM. Localization of CXCR4 in the forebrain of the adult rat. Brain Research. 2010 Feb 22;1315:53-62.

5. Trecki J, Unterwald EM. Modulation of cocaine-induced activity by intracerebral administration of CXCL12. Neuroscience. 2009 Jun 16;161(1):13-22.

6. Gentile D, **Trecki J**, Patel A, Fausnight T, Angelini B, Skoner D. Effect of tetanus immunization on t-helper cytokine production in adults with and without allergic rhinitis. Allergy and Asthma Proceedings. 2006 May-June; 27(3): 197-201(5).

7. Dambach MJ, **Trecki J**, Markovitz NS. Oncolytic viruses derived from the γ34.5-deleted Herpes simplex virus R3616 encode a truncated UL3 protein. Molecular Therapy. 2006 May; 13(5):891-8.

8. Gentile DA, Schreiber R, Howe-Adams J, **Trecki J**, Patel A, Angelini B, Skoner DP. Diminished dendritic cell interleukin 10 production in atopic children. Ann Allergy Asthma Immunol. 2004 May;92(5):538-44.

9. Gentile DA, Doyle WJ, Zeevi A, Howe-Adams J, **Trecki J**, Skoner DP. Association between TNF-α and TGF-β genotypes in infants and parental history of allergic rhinitis and asthma. Hum. Immunol. 2004 Apr; 65(4):347-51.

10. Gentile D, Howe-Adams J, **Trecki J**, Patel A, Angelini B, Skoner DP. Association between environmental tobacco smoke and diminished dendritic cell interleukin 10 production during infancy. Ann Allergy Asthma Immunol. 2004 Apr; 92(4):433-7.

11. Gentile DA, Doyle WJ, Zeevi A, Howe-Adams J, Kapadia S, **Trecki J**, Skoner DP: Cytokine gene polymorphisms moderate illness severity in infants with respiratory syncytial virus infection. Hum Immunol. 2003 Mar; 64(3):338-44.

ABSTRACTS, POSTERS & INVITED TALKS AT SCIENTIFIC SYMPOSIA

PUBLISHED ABSTRACTS:

1. Kapadia SB, Gentile DA, Howe-Adams J, **Trecki J**, Skoner DP. Relationship between local TNF protein levels and severity of illness during respiratory syncytial virus infection in hospitalized infants. J Allergy Clin Immunol 2002; 109:S341.

2. Schreiber RL, Gentile DA, Howe-Adams J, **Trecki J**, Patel A, Fireman P, Skoner DP. Diminished dendritic cell (DC) IL-10 production in children with allergic rhinitis (AR) and/or asthma. J Allergy Clin Immunol 2003; 111(2):S188.

3. Howe-Adams J, Gentile DA, Zeevi A, **Trecki J**, Angelini BL, Skoner DP. Cytokine gene polymorphisms moderate illness severity in infants with respiratory syncytial virus (RSV) infection. J Allergy Clin Immunol 2003; 111(2):S270.

4. Gentile DA, Howe-Adams J, **Trecki J**, Patel A, Fireman P, Skoner DP. Diminished dendritic cell (DC) IL-10 production and enhanced T helper lymphocyte type 2 (Th2) cytokine responses during infancy. J Allergy Clin Immunol 2003; 111(2):S280.

5. Otte R, Gentile D, Angelini B, Krahnke J, Richards H, **Trecki J**, Doyle W, Skoner D. Effect of levalbuterol on exhaled nitric oxide (NO) levels in asthmatic subjects. J Allergy Clin Immunol. 2004;113(Suppl):S32-S33.

POSTER PRESENTATIONS:

1. Diminished DC IL-10 production and enhanced Th2 cytokine responses during infancy. Pediatric Academic Societies' Annual Meeting. May 2003, Seattle, WA.

2. Behavioral effects of cocaine are enhanced by stromal cell derived factor 1 (SDF-1) in rats. Mid-Atlantic Pharmacology Society Meeting. October 2005. Philadelphia, PA.

3. Behavioral effects of cocaine are enhanced by stromal cell derived factor 1 (SDF-1) in rats. The College on Problems of Drug Dependence, Scottsdale, AZ, June 2006.

4. SDF-1α potentiates the behavioral activity in rats. The College on Problems of Drug Dependence, Quebec City, Canada, June 2007.

5. CXCL12 potentiates the behavioral activity in rats. Mid-Atlantic Pharmacology Society Annual Meeting, Philadelphia, PA, October 2007.

6. Behavioral effects of cocaine are enhanced by CXCL12 in rats. Society for Neuroscience, San Diego, CA, November 2007.

7. The effects of CXCL12 on cocaine within the mesolimbic dopamine pathway. Philadelphia Chapter for the Society of Neuroscience, Philadelphia, PA, February 2008.

ORAL PRESENTATIONS:

1. The effects of CXCL12 on cocaine within the mesolimbic dopamine pathway. College on Problems of Drug Dependence, San Juan, Puerto Rico, June 2008.

2. The Modulation of the Mesolimbic and Nigrostriatal Dopamine Pathways by CXCL12 and CXCR4. Society for Neuroscience Annual Meeting, Washington, DC, Nov. 2008

3. Current Techniques in Behavioral Pharmacology. Directors Meeting, Society for Neuroscience, Washington, DC, Sept. 2009

4. Statistical Significance versus Biological Relevance: A Case Study in Neurobehavioral Testing. Neurobehavioral Teratology Society. Baltimore, MD, June 2012

MEMBERSHIP IN PROFESSIONAL SOCIETIES

Center for Substance Abuse Research, 2004-2009

College on Problems of Drug Dependence, 2004-2009

The American Society for Pharmacology and Experimental Therapeutics, Chapter - Mid-Atlantic Pharmacology Society, 2004-2009

Society for Neuroscience, 2004-present
Committee Member – Membership & Chapters Committee, Society for Neuroscience; 2012-present

DECLARATION OF JORDAN TRECKI, PH.D.

I, Jordan Trecki, declare and say:

1. I am an employee of the United States Department of Justice, Drug Enforcement Administration (DEA). I have been employed by DEA as a Pharmacologist since August 2012.
2. One of my primary responsibilities as a Pharmacologist at DEA's Drug and Chemical Evaluation Section (ODE) is to review drugs and other substances for possible control under the Controlled Substances Act (CSA).
3. Since joining ODE, I have reviewed a number of drugs and other substances and have prepared scheduling review documents for control under the CSA.
4. In my capacity as a Pharmacologist, I make the following statements regarding the pharmacological evaluation of the substances UR-144 and XLR11.
5. Classical cannabinoids, such as the primary psychoactive constituent of marijuana, Δ9-tetrahydrocannabinol (Δ9-THC) produce pharmacological effects via specific receptors in the body. The complex effects of cannabinoids are considered to be mediated through at least two distinct G protein-coupled transmembrane receptors designated as CB1 and CB2. The CB1 receptors are found predominantly in the central nervous system, and are responsible for most of the overt pharmacological effects including the euphoric and psychoactive effects (Wells and Ott, 2011) of cannabinoid agonists. The CB2 receptors are found primarily in the periphery and expressed in the immune system.

UR-144

6. UR-144 is a synthetic cannabinoid. UR-144 has cannabinoid-like effects on the central nervous system that are substantially similar to the cannabinoid effects on the central nervous system of JWH-018, a CSA Schedule I cannabinoid substance. This is based on the following information:
    a. UR-144 binds to CB1 receptor with a reported binding affinity (Ki) of 150 nM (Frost et al., 2010). Another study shows that UR-144 binds to the

CB1 receptor with an apparent Ki value of 28.9 nM (RTI, January 31st 2013). JWH-018 binds to the CB1 receptor with a reported binding affinity (Ki) of 9.0 nM (Aung et al., 2000).

b. UR-144 is an agonist at the CB1 receptor with a reported EC50 of 1295 nM (Perkin Elmer, 2013a; provided to DEA January 15th, 2013). JWH-018 is also an agonist at the CB1 receptor with a reported EC50 of 4.4 nM (DEA, 2012, Atwood et al., 2010).

c. UR-144 substituted fully (ED50 = 7.1 µmol/kg, 30 minutes before testing) for the discriminative stimulus effects of THC in mice trained to discriminate 5.6 mg/kg of THC from vehicle control. Full substitution occurred at a dose (5.6 mg/kg) that did not alter response rate (RTI, January 31st 2013). JWH-018 was previously found to also substitute fully (ED50 = 0.39 mg/kg) for the discriminative stimulus effects produced by 3 mg/kg of THC in rats. (Forster et al., 2011). This means that mice and rats trained to recognize the psychoactive effects of THC recognize both UR-144 and JWH-018 as having the same psychoactive effects as THC.

d. Preliminary data from a different drug discrimination study was provided to DEA by NIDA showing that UR-144 fully substituted for THC in 3 rats at 5 mg/kg (the only dose tested so far) in an ongoing study (NIDA, personal communication to DEA, January 30th 2013). These preliminary results are consistent with the other drug discrimination results presented above.

7. Based on my review of the available information regarding UR-144, I hereby conclude that UR-144 produces pharmacological effects that are substantially similar to those of the Schedule I cannabinoid JWH-018.

XLR11

8. XLR11 is a synthetic cannabinoid. XLR11 has cannabinoid-like effects on the central nervous system that are substantially similar to the cannabinoid effects on the central

nervous system of JWH-018, a CSA Schedule I cannabinoid substance. This is based on the following information:

a. Binding of XLR11 was assessed in a HEK-293 membrane preparation. XLR11 was shown to bind to the CB1 receptor with an apparent Ki value of 24.2 nM (RTI, 2013). JWH-018 binds to the CB1 receptors with reported binding affinity (Ki) of 9.0 nM (Aung *et al.*, 2000).

b. XLR11 is an agonist at the CB1 receptor with a reported EC50 of 359 nM (Perkin Elmer, 2013b; provided to DEA January 15th, 2013). JWH-018 is also an agonist at the CB1 receptor with a reported EC50 of 4.4 nM (DEA, 2012, Atwood et al., 2010).

c. XLR11 substituted fully (ED50 = 3.3 µmol/kg, 30 minutes before testing) for the discriminative stimulus effects of THC in mice trained to discriminate 5.6 mg/kg of THC from vehicle control. Full substitution occurred at a dose (3 mg/kg) that did not alter response rate (RTI, 2013). JWH-018 was previously found to also substitute fully (ED50 = 0.39 mg/kg) for the discriminative stimulus effects produced by 3 mg/kg of THC in rats. (Forster et al., 2011). This means that mice and rats trained to recognize the psychoactive effects of THC recognize both XLR-11 and JWH-018 as having the same psychoactive effects as THC.

9. Based on my review of all the available information regarding XLR11, I hereby conclude that XLR11 produces pharmacological effects that are substantially similar to those of the Schedule I cannabinoid JWH-018.

References

1. 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.

2. 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.

3. Perkin Elmer (2013a). **Cannabinoid, CB1 (h) Agonist Cellular/Functional Assay. TDP# UR144.** NIDA Contract N01DA-8-8877.

4. Perkin Elmer (2013b). **Cannabinoid, CB1 (h) Agonist Cellular/Functional Assay. TDP# XLR11.** NIDA Contract N01DA-8-8877.

5. DEA (2012). **DEA Background, Data, and Analysis of Five Synthetic Cannabinoids – February 2012.** Federal Register Docket ID DEA-2012-0001-0002. Available on regulations.gov.

6. Frost JM, Dart MJ, Tietje KR, Garrison TR, Grayson GK, Daza AV, El-Kouhen OF, Yao BB, Hsieh GC, Pai M, Zhu CZ, Chandran P, and Meyer MD (2010). **Indol-3-ylcycloalkyl ketones: effects of N1 substituted indole side chain variations on CB2 cannabinoid receptor activity.** *Journal of Medicinal Chemistry* 53:295-315.

7. Forster MJ, Gatch MB, Taylor CM (2011). **JWH-018. Test of substitution for the discriminative stimulus effects of Delta(9)-THC.** Contract: N01DA-7-8872

8. RTI International (2013). **In Vitro and In Vivo Abuse Liability Testing of (1-(5-fluoropentyl)-1H-indol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone and (1-pentyl-1H-indol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone.** RTI Technical Report. RTI Project No. 0213753. Sponsored by United States Drug Enforcement Administration.

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

DECLARATION OF JORDAN TRECKI, PH.D.

I declare under penalty of perjury that the foregoing statements are true and accurate to the best of my knowledge and belief.

Dated: February 22, 2013

Jordan Trecki, Ph.D.
Pharmacologist,
Office of Diversion Control
Drug Enforcement Administration

[Federal Register Volume 78, Number 71 (Friday, April 12, 2013)]
[Proposed Rules]
[Pages 21858-21861]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2013-08671]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-373]

Schedules of Controlled Substances: Temporary Placement of Three Synthetic Cannabinoids Into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of Intent.

SUMMARY: The Deputy Administrator of the Drug Enforcement Administration (DEA) is issuing this notice of intent to temporarily schedule three synthetic cannabinoids into the Controlled Substances Act (CSA) pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). The substances are 1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (UR-144), 1-(5-fluoro-pentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoro-UR-144; XLR11) and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA, AKB48). This action is based on a finding by the Deputy Administrator that the placement of these synthetic cannabinoids into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. Any final order will be published in the Federal Register and may not be issued prior to May 13, 2013. Any final order will impose the administrative, civil, and criminal sanctions and regulatory controls of Schedule I substances under the CSA on the manufacture, distribution, possession, importation, and exportation of these synthetic cannabinoids.

FOR FURTHER INFORMATION CONTACT: John W. Partridge, Executive Assistant, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152, telephone (202) 307-7165.

SUPPLEMENTARY INFORMATION:

Background

Section 201 of the CSA (21 U.S.C. 811) provides the Attorney General with the authority to temporarily place a substance into Schedule I of the CSA for two years without regard to the requirements of 21 U.S.C. 811(b) if he finds that such action is necessary to avoid imminent hazard to the public safety. 21 U.S.C. 811(h). In addition, if

proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1), the Attorney General may extend the temporary scheduling up to one year.

Where the necessary findings are made, a substance may be temporarily scheduled if it is not listed in any other schedule under section 202 of the CSA (21 U.S.C. 812) or if there is no exemption or approval in effect under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) for the substance. The Attorney General has delegated his authority under 21 U.S.C. 811 to the Administrator of DEA, who in turn has delegated her authority to the Deputy Administrator of DEA. 28 CFR 0.100, Appendix to Subpart R.

Section 201(h)(4) of the CSA (21 U.S.C. 811(h)(4)) requires the Deputy Administrator to notify the Secretary of the Department of Health and Human Services (HHS) of his intention to temporarily place a substance into Schedule I of the CSA.\1\ The Deputy Administrator has transmitted notice of his intent to place UR-144, XLR11, and AKB48 in Schedule I on a temporary basis to the Assistant Secretary by letter dated February 14, 2013. The Assistant Secretary responded to this notice by letter dated March 14, 2013 (received by DEA on March 21, 2013), and advised that based on review by the Food and Drug Administration (FDA), there are currently no investigational new drug applications or approved new drug applications for UR-144, XLR11, or AKB48. The Assistant Secretary also stated that HHS has no objection to the temporary placement of UR-144, XLR11 or AKB48 into Schedule I of the CSA. DEA has taken into consideration the Assistant Secretary's comments. As UR-144, XLR11, and AKB48 are not currently listed in any schedule under the CSA, and as no exemptions or approvals are in effect for UR-144, XLR11, and AKB48 under Section 505 of the FD&C Act (21 U.S.C. 355), DEA believes that the conditions of 21 U.S.C. 811(h)(1) have been satisfied. Any additional comments submitted by the Assistant Secretary in response to this notification shall also be taken into consideration before a final order is published. 21 U.S.C. 811(h)(4).

\1\ Because the Secretary of the Department of Health and Human Services (HHS) has delegated to the Assistant Secretary for Health the Department of Health and Human Services the authority to make domestic drug scheduling recommendations, for purposes of this Notice of Intent, all subsequent references to ``Secretary'' have been replaced with ``Assistant Secretary.'' As set forth in a memorandum of understanding entered into by HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the Controlled Substance Act (CSA), with the concurrence of NIDA. 50 FR 9518.

To make a finding that placing a substance temporarily into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Deputy Administrator is required to consider three of the eight factors set forth in section 201(c) of the CSA (21 U.S.C. 811(c)). These factors are as follows: the substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(c)(4)-(6). Consideration of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

A substance meeting the statutory requirements for temporary scheduling (21 U.S.C. 811(h)(1)) may only be placed in Schedule I. Substances in Schedule I are those that have a high potential for

abuse, no currently accepted medical use in treatment in the United States (U.S.), and a lack of accepted safety for use under medical supervision. 21 U.S.C. 812(b)(1). Available data and information for UR-144, XLR11, and AKB48 indicate that these three synthetic cannabinoids have a high potential for abuse, no currently accepted medical use in treatment in the U.S., and a lack of accepted safety for use under medical supervision.

Synthetic Cannabinoids

While synthetic cannabinoids have been developed over the last 30 years for research purposes to investigate the cannabinoid system, no scientific literature referring to UR-144, XLR11 or AKB48 was available prior to these drugs identification in the illicit market. In addition, no legitimate non-research uses have been identified for these synthetic cannabinoids nor have they been approved by FDA for human consumption. These synthetic cannabinoids, of which 1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (UR-144), 1-(5-fluoro-pentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoro-UR-144; XLR11), and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA, AKB48) are representative, are so-termed for their [Delta]\9\-tetrahydrocannabinol (THC)--like

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pharmacological properties. Numerous herbal products have been analyzed, and UR-144, XLR11, and AKB48 have been identified, in varying mixture profiles and amounts, spiked on plant material.

From January 2009 through January 24, 2013, according to the System to Retrieve Information from Drug Evidence (STRIDE) data, there are 1,074 reports involving 137 cases for UR-144, 773 reports involving 134 cases for XLR11, and 66 reports involving 25 cases for AKB48. From March 2010 to January 29, 2013, the National Forensic Laboratory Information System (NFLIS) registered 9,346 reports containing these synthetic cannabinoids (UR-144--4,387 reports; XLR11--4,516 reports; AKB48--443 reports) across 32 states. No instances regarding UR-144, XLR11 or AKB48 were reported in NFLIS prior to March of 2010. Collectively, reports from NFLIS and (STRIDE) \2\ (11,259 reports total through January 29, 2013) for UR-144, XLR11 and AKB48 have exceeded the number of reports for the five synthetic cannabinoid substances (JWH-018, JWH-200, JWH-073, CP-47,497 and CP-47,497 C8 homologue [cannabicyclohexanol]) (7,340 total reports through December 31, 2012). JWH-018, JWH-200, JWH-073, CP-47,497 and CP-47,497 C8 homologue were temporarily scheduled on March 1, 2011, and later placed in Schedule I by Section 1152 of Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112-144, on July 9, 2012. Section 1152 of the FDASIA \3\ amended the CSA by placing cannabimimetic agents and 26 specific substances (including 15 synthetic cannabinoids, 2 synthetic cathinones, and 9 phenethylamines of the 2C-series) in Schedule I. UR-144, XLR11, and AKB48 were not included among the 15 specific named synthetic cannabinoids, and do not fall under the definition of cannabimimetic agents, under FDASIA.

\2\ National Forensic Laboratory Information System (NFLIS) is a program sponsored by Drug Enforcement Administration's (DEA) Office of Diversion Control which compiles information on exhibits analyzed in State and local law enforcement laboratories. System to Retrieve Information from Drug Evidence (STRIDE) is a DEA database which compiles information on exhibits analyzed in DEA laboratories.

\3\ Subtitle D of Title XI of the Food and Drug Administration Safety and Innovation Act (FDASIA), which includes Sections 1151-1153 of Pub. L. 112-144, is also known as the ``Synthetic Drug Abuse Prevention Act of 2012,'' or ``SDAPA.''

Factor 4. History and Current Pattern of Abuse

Synthetic cannabinoids laced on plant material were first reported in the U.S. in December 2008, when a shipment of `Spice' was seized and analyzed by U.S. Customs and Border Patrol in Dayton, Ohio. Also in December 2008, JWH-018 and cannabicyclohexanol were identified by German forensic laboratories.

Since the initial identification of JWH-018 (December 2008), many additional synthetic cannabinoids with purported psychotropic effects have been found laced on plant material or related products. The popularity of these synthetic cannabinoids and their associated products appears to have increased since January 2010 in the U.S. based on seizure exhibits and media reports. This trend appears to mirror that experienced in Europe since 2008. Synthetic cannabinoids are being encountered in several regions of the U.S. with the substances primarily found as adulterants on plant material products as self-reported on internet discussion boards. Since then, numerous other synthetic cannabinoids including UR-144, XLR11 and AKB48 have been identified as product adulterants.

Data gathered from published studies, supplemented by discussions on Internet discussion Web sites and personal communications with toxicological testing laboratories, demonstrate that products laced with UR-144, XLR11 and/or AKB48 are being abused mainly by smoking for their psychoactive properties. The adulterated products are marketed as `legal' alternatives to marijuana. This characterization, along with their reputation as potent herbal intoxicants, has increased their popularity. Several synthetic cannabinoids have been shown to display higher potency in vitro when compared to THC. Smoking mixtures of these substances for the purpose of achieving intoxication has been identified as a reason for numerous emergency room visits and calls to poison control centers. Abuse of these synthetic cannabinoids and their products has been characterized with both acute and long term public health and safety issues. In addition, numerous states, local jurisdictions, and the international community have controlled these substances.

Factor 5. Scope, Duration and Significance of Abuse

According to forensic laboratory reports, the first appearance of synthetic cannabinoids in the U.S. occurred in November 2008, when U.S. Customs and Border Protection analyzed ``Spice'' products. NFLIS has reported 9,346 exhibits (March 2010 to January 29, 2013) related to UR-144, XLR11 and AKB48 from various states including Alaska, Alabama, Arkansas, California, Colorado, Florida, Georgia, Iowa, Indiana, Illinois, Kansas, Kentucky, Louisiana, Maryland, Minnesota, Missouri, New Hampshire, New Jersey, New Mexico, North Dakota, Nebraska, Nevada, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Virginia, Wisconsin and Wyoming. STRIDE has reported 1,913 records involving UR-144, XLR11 and AKB48 from January 2009 through January 24, 2013. From January 1 through December 31, 2012, the American Association of Poison Control Centers \4\ has reported receiving in excess of 5,200 calls relating to products purportedly laced with synthetic cannabinoids. Although the center does not identify specific cannabinoid substances, the data does indicate the magnitude of

exposure to synthetic cannabinoids.

\4\ American Association of Poison Control Centers (AAPCC) is a non-profit, national organization that represents the poison centers of the United States.

Factor 6. What, If Any, Risk There Is to the Public Health

UR-144, XLR11 and AKB48 are pharmacologically similar to Schedule I substances THC and JWH-018, as well as other synthetic cannabinoids. By sharing pharmacological similarities with the Schedule I substances (THC and JWH-018), synthetic cannabinoids pose a risk to the abuser. In addition, the chronic abuse of products laced with synthetic cannabinoids has also been linked to addiction and withdrawal. Law enforcement, military, and public health officials have reported exposure incidents that demonstrate the dangers associated with abuse of synthetic cannabinoids to both the individual abusers and other affected individuals since these substances were never intended for human use. Warnings regarding the dangers associated with abuse of synthetic cannabinoids and their products have been issued by numerous state public health departments and poison control centers and private organizations. In a 2012 report, the Substance Abuse and Mental Health Services Administration \5\ reported 11,406 emergency department visits involving a synthetic cannabinoid product during 2010.

\5\ Substance Abuse and Mental Health Services Administration (SAMHSA) is a branch of the U.S. Department of Health and Human Services (HHS). It is charged with improving the quality and availability of prevention, treatment, and rehabilitative services in order to reduce illness, death, disability, and cost to society resulting from substance abuse and mental illnesses.

Detailed product analyses have detected variations in the amount and type of synthetic cannabinoid laced on plant material even within samplings of

[[Page 21860]]

the same product. Since abusers obtain these drugs through unknown sources, purity of these drugs is uncertain, thus posing significant adverse health risk to these users. Submissions to DEA laboratories from January 2012 through February 11, 2013, have documented over 142 distinct packaging examples containing a mixture of UR-144, XLR11 and/or AKB48. These unknown factors present a significant risk of danger to the abuser. Some of the adverse health effects reported in response to the abuse of synthetic cannabinoids include vomiting, anxiety, agitation, irritability, seizures, hallucinations, tachycardia, elevated blood pressure, and loss of consciousness. As mentioned above, there are reported instances of emergency department admissions in association with the abuse of these THC-like substances. There are no recognized therapeutic uses of these substances in the U.S.

In February 2013, the Centers for Disease Control and Prevention published a report by Murphy et al. describing unexplained cases of acute kidney injury in 16 patients, all of whom had reported recent smoking of synthetic cannabinoids. Upon further investigation, it was determined that of the 16 patients, 7 of the subjects had smoked

substances that were positive for XLR11 or its metabolite. Cases were reported from Wyoming (4 cases), Rhode Island (1 case), New York (2 cases), Oregon (6 cases), Kansas (1 case) and Oklahoma (2 cases).

Finding of Necessity of Schedule I Scheduling To Avoid Imminent Hazard to Public Safety

Based on the above data and information, the continued uncontrolled manufacture, distribution, importation, exportation, and abuse of UR-144, XLR11, and AKB48 pose an imminent hazard to the public safety. DEA is not aware of any currently accepted medical uses for these synthetic cannabinoids in the U.S. A substance meeting the statutory requirements for temporary scheduling (21 U.S.C. 811(h)(1)) may only be placed in Schedule I. Substances in Schedule I are those that have a high potential for abuse, no currently accepted medical use in treatment in the U.S., and a lack of accepted safety for use under medical supervision. Available data and information for UR-144, XLR11, and AKB48 indicate that these three synthetic cannabinoids have a high potential for abuse, no currently accepted medical use in treatment in the U.S., and a lack of accepted safety for use under medical supervision. As required by section 201(h)(4) of the CSA (21 U.S.C. 811(h)), the Deputy Administrator through a letter dated February 14, 2013, notified the Assistant Secretary of Health of the intention to temporarily place these three synthetic cannabinoids in Schedule I.

Conclusion

This notice of intent initiates expedited temporary scheduling action and provides the 30-day notice pursuant to section 201(h) of the CSA (21 U.S.C. 811(h)). In accordance with the provisions of section 201(h) of the CSA (21 U.S.C. 811(h)), the Deputy Administrator has considered available data and information and has set forth herein the grounds for his determination that it is necessary to temporarily schedule three synthetic cannabinoids, 1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone (UR-144), 1-(5-fluoro-pentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoro-UR-144; XLR11), and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA, AKB48) in Schedule I of the CSA and finds that placement of these synthetic cannabinoids into Schedule I of the CSA is warranted in order to avoid an imminent hazard to the public safety.

Because the Deputy Administrator hereby finds that it is necessary to temporarily place these synthetic cannabinoids into Schedule I to avoid an imminent hazard to the public safety, any subsequent final order temporarily scheduling these substances will be effective on the date of publication in the Federal Register, and will be in effect for a period of up to three years pending completion of the permanent or regular scheduling process. It is the intention of the Deputy Administrator to issue such a final order as soon as possible after the expiration of 30 days from the date of publication of this notice. UR-144, XLR11, and AKB48 will then be subject to the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, possession, importing and exporting of a Schedule I controlled substance under the CSA.

Regular scheduling actions in accordance with 21 U.S.C. 811(a) are subject to formal rulemaking procedures done ``on the record after opportunity for a hearing'' conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth specific criteria for scheduling a drug or other substance. While temporary scheduling orders are not subject to judicial review (21 U.S.C. 811(h)(6)), the regular scheduling process of formal rulemaking affords interested parties with

appropriate process and the government with any additional relevant information needed to make a determination. Final decisions which conclude the regular scheduling process of formal rulemaking are subject to judicial review. 21 U.S.C. 877.

Regulatory Matters

Section 201(h) of the CSA (21 U.S.C. 811(h)) provides for an expedited temporary scheduling action where such action is necessary to avoid an imminent hazard to the public safety. As provided in this subsection, the Attorney General may, by order, schedule a substance in schedule I on a temporary basis. Such an order may not be issued before the expiration of 30 days from (1) the publication of a notice in the Federal Register of the intention to issue such order and the grounds upon which such order is to be issued, and (2) the date that notice of a proposed temporary scheduling order is transmitted to the Secretary of HHS. 21 U.S.C. 811(h)(1).

Inasmuch as section 201(h) of the CSA directs that temporary scheduling actions be issued by order and sets forth the procedures by which such orders are to be issued, DEA believes that the notice and comment requirements of section 553 of the Administrative Procedure Act (APA) (5 U.S.C. 553) do not apply to this notice of intent. In the alternative, even assuming that this notice of intent might be deemed to be subject to section 553 of the APA, the Deputy Administrator finds that there is good cause to forgo the notice and comment requirements of section 553, as any further delays in the process for issuance of temporary scheduling orders would be impracticable and contrary to the public interest in view of the manifest urgency of the temporary scheduling action to avoid an imminent hazard to the public safety.

Although this notice of intent to issue a temporary scheduling order is not subject to the notice and comment requirements of section 553 of the APA, DEA notes that in accordance with 21 U.S.C. 811(h)(4), the Deputy Administrator will be taking into consideration any comments submitted by the Secretary of HHS with regard to the proposed temporary scheduling order. Further, DEA believes that this temporary scheduling action is not a ``rule'' as defined by 5 U.S.C. 601(2), and, accordingly, not subject to the requirements of the Regulatory Flexibility Act. The requirements for the preparation of an initial regulatory flexibility analysis in 5 U.S.C. 603(a) are not applicable where (as here) the agency is not required by section 553 of

[[Page 21861]]

the APA or any other law to publish a general notice of proposed rulemaking.

Additionally, this action is not a significant regulatory action as defined by Executive Order 12866 ``Regulatory Planning and Review'', section 3(f), and, accordingly, this action has not been reviewed by the Office of Management and Budget.

This action will not have substantial direct effects on the States, on the relationship between the national government and the States, or on distribution of power and responsibilities among the various levels of government. Therefore, in accordance with Executive Order 13132 ``Federalism'' it is determined that this action does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control,

Reporting and recordkeeping requirements.

Under the authority vested in the Attorney General by section 201(h) of the CSA (21 U.S.C. 811(h)), and delegated to the Deputy Administrator of the DEA by Department of Justice regulations (28 CFR 0.100, Appendix to Subpart R), the Deputy Administrator hereby intends to order that 21 CFR Part 1308 be amended as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

0
1. The authority citation for Part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

0
2. Section 1308.11 is amended by adding new paragraphs (h)(9), (10), and (11) to read as follows:

Sec. 1308.11 Schedule I.

* * * * *

(h) * * *

(9) 1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone, its optical, positional, and geometric isomers, salts and salts of isomers--7144 (Other names: UR-144, 1-pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole)

(10) 1-(5-fluoro-pentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone, its optical, positional, and geometric isomers, salts and salts of isomers--7011 (Other names: 5-fluoro-UR-144, 5-F-UR-144, XLR11, 1-(5-fluoro-pentyl)-3-(2,2,3,3-tetramethylcyclopropoyl)indole)

(11) N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide, its optical, positional, and geometric isomers, salts and salts of isomers--7048 (Other names: APINACA, AKB48)

Dated: April 5, 2013.
Thomas M. Harrigan,
Deputy Administrator.
[FR Doc. 2013-08671 Filed 4-11-13; 8:45 am]
BILLING CODE 4410-09-P

PRESS RELEASE

April 3, 2013

Lac du Flambeau Band of Lake Superior Chippewa Indians Declares State of Emergency.

Lac du Flambeau, Wisconsin – The Lac du Flambeau Band of Lake Superior Chippewa Indians Tribal Council declared a State of Emergency on March 29, 2013 as it relates to the threat of synthetic cannabinoids, synthetic cathinones and other illegal drugs affecting the Reservation and Tribal Members. Due to the rising popularity and proliferation of synthetic cannabinoids, synthetic cathinones and other illegal drugs within the Tribal Nation and surrounding community, the Tribal Council is taking decisive action against the new wave of drugs commonly referred to as K2, Spice, Potpourri, Bath Salts and Plant Food. The Tribal Council recognizes that Indian Country cannot remain idle when national reports and scientific information repeatedly publish that many first-time and repeat users are under the misconception that synthetic cannabinoids and synthetic cathinones are legal and/or safe when, in fact, they are not. Common side effects from a single use of synthetic cannabinoids include: hallucinations, panic attacks, anxiety, paranoia, agitation, extreme anger, seizure, tremors, kidney failure, liver failure, increased heart rate, elevated blood pressure, stroke, coma, and death. Due to the great irreparable harm and permanent effects that can result from using synthetic cannabinoids, synthetic cathinones and other illegal drugs, the Tribal Council is committing the necessary Tribal resources to rid the Reservation and the surrounding community of this catastrophic menace that will not only entail swift prosecution but will also include a Tribal campaign focused on prevention and a committed Tribal effort to provide extensive rehabilitation services. The Tribal Council remains firm that every Tribal department will partake in the war against synthetic cannabinoids, synthetic cathinones and other illegal drugs. As detailed in the Tribal Council Resolution, the Lac du Flambeau Tribe is dedicated to following extensive and comprehensive changes to return the Tribal Nation to the teachings of our ancestors:

- Restructuring the Tribal Code to criminalize synthetic cannabinoids and synthetic cathinones;
- Working with federal, local and state governments to ensure offenders are prosecuted;
- Treatment and rehabilitation for those who have become addicted to synthetic cannabinoids and synthetic cathinones;
- Revising the Tribal Housing Regulations and Policies to implement drug tests for tenants;
- Banishment, Disenrollment and/or Forfeiture of *Per Capita* payments for those caught using, selling and/or manufacturing synthetic cannabinoids and synthetic cathinones;
- Review of current and future grant funding specific to substance abuse prevention and intervention to specifically target this developing problem;
- Mobilize existing "community-based" task forces to participate in door to door distribution of prevention materials and begin community education; and,
- Introduction of an educational campaign in community schools and youth programs.

Turtle Talk

BY MATTHEW L.M. FLETCHER | APRIL 3, 2013 · 11:12 AM

Lac Du Flambeau Declares State of Emergency — Synthetic and Illegal Drugs

Lac du Flambeau Band of Lake Superior Chippewa Indians Declares State of Emergency (2013 04 03 LDF Press Release LDF State of Emergency re Synthetic and Illegal Drugs FINAL).

Lac du Flambeau, Wisconsin – The Lac du Flambeau Band of Lake Superior Chippewa Indians Tribal Council declared a State of Emergency on March 29, 2013 as it relates to the threat of synthetic cannabinoids, synthetic cathinones and other illegal drugs affecting the Reservation and Tribal Members. Due to the rising popularity and proliferation of synthetic cannabinoids, synthetic cathinones and other illegal drugs within the Tribal Nation and surrounding community, the Tribal Council is taking decisive action against the new wave of drugs commonly referred to as K2, Spice, Potpourri, Bath Salts and Plant Food. The Tribal Council recognizes that Indian Country cannot remain idle when national reports and scientific information repeatedly publish that many first-time and repeat users are under the misconception that synthetic cannabinoids and synthetic cathinones are legal and/or safe when, in fact, they are not. Common side effects from a single use of synthetic cannabinoids include: hallucinations, panic attacks, anxiety, paranoia, agitation, extreme anger, seizure, tremors, kidney failure, liver failure, increased heart rate, elevated blood pressure, stroke, coma, and death. Due to the great irreparable harm and permanent effects that can result from using synthetic cannabinoids, synthetic cathinones and other illegal drugs, the Tribal Council is committing the necessary Tribal resources to rid the Reservation and the surrounding community of this catastrophic menace that will not only entail swift prosecution but will also include a Tribal campaign focused on prevention and a committed Tribal effort to provide extensive rehabilitation services. The Tribal Council remains firm that every Tribal department will partake in the war against synthetic cannabinoids, synthetic cathinones and other illegal drugs. As detailed in the Tribal Council Resolution, the Lac du Flambeau Tribe is dedicated to following extensive and comprehensive changes to return the Tribal Nation to the teachings of our ancestors:

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- Review of current and future grant funding specific to substance abuse prevention and intervention to specifically target this developing problem;

Follow

- Mobilize existing "community-based" task forces to participate in door to door distribution of prevention materials and begin community education; and,
- Introduction of an educational campaign in community schools and youth programs.

4 Responses to *Lac Du Flambeau Declares State of Emergency — Synthetic and Illegal Drugs*

DG
April 3, 2013 at 3:10 pm

Awesome! Good job LDF!

Reply

Tory Williams(1446)
April 3, 2013 at 6:21 pm

WOW IT'S ABOUT TIME THE TRIBE DOES SOMETHING ABOUT THAT DRUG PROBLEM ON THE RESERVATION THERE HAS BEEN SOME DEATHS RELATED TO THESE DRUGS OF OUR TRIBAL MEMBERS...

Reply

mlblogsindiansailabilityams
April 4, 2013 at 7:39 pm

Problem is that the Republican State of Wisconsin is still fighting the French&Indian War. This dose nothing for economic development and certainly the tribe dose not care about sending someone to the Paraolympic games in Rio 2016. If they were serious about this, start a sailability on the lake despite the Republican Rednecks and take over the lake. I think governor Walker wants a shooting war to get more funding. Tribal

police can take over that lake since Walker said that his State is BROKE. When are we going to see some DISABLED NATIVE AMERICANS entering the Milwaukee National Disabled Sailing Championship or are they going to follow Morongo dis-enrolling everyone and extinguish the tribe.

Reply

Diane Ellis

April 3, 2013 at 11:37 pm

You all are in my prayers. As a recovering addict of ten years and a substance abuse counselor, I see this problem ever increasing. May our Creator hold each one effected by these substances (and others) in the palm of his hand.

Reply

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