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SENTENCING POLICY FOR SYNTHETIC DRUGS

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I. Introduction

Judge Pryor and members of the Sentencing Commission: Thank you for holding this hearing today and for providing the opportunity to discuss the threat posed by and trafficking patterns associated with the illicit manufacturing and distribution of synthetic drugs, or what are often refer to as new psychoactive substances (NPS).

The trafficking and use of NPS continues to be a challenge for public health and law enforcement. The recreational use of NPS is associated with high levels of abuse and toxicity. These substances continue to be introduced into drug markets as replacements for traditional controlled substances and pose a great risk to the public due to both their often predictable and unpredictable health effects. While NPS challenges increase, there has been a resurgence in MDMA use and availability, presenting additional challenges for public health and law enforcement. Some drug markets have witnessed an increase in MDMA content in tablets; in the United States we have witnessed an increase, decrease, then leveling off of MDMA drug seizures. Drug seizure data demonstrate MDMA is still a popular drug of abuse and being encountered regularly by law enforcement. The scientific information continues to demonstrate MDMA is a threat to public health and safety due to its pharmacological effects and abuse.

In many instances, new psychoactive substances were initially used as research tools to investigate biological systems such as endogenous neurotransmitter systems. This is particularly true of the synthetic cannabinoids JWH-018 and AM-2201. These two substances, having higher potency than Δ9-tetrahydrocannabinol (THC) at the cannabinoid receptors, were initially part of research programs before being used illicitly for their psychoactive effects. Two of the drug classes that rapidly emerged on the illicit drug market were the synthetic cannabinoids and the synthetic cathinones. Due to deceptive marketing, users may have mistakenly perceived them as safe alternatives to traditional drugs of abuse. The arising problems from the introduction of improperly tested substances prompted regulatory control to protect the public from those preying on vulnerable populations. In many cases, use is directly linked to harmful events, including emergency medical intervention, dependence, and death. As a result, serious adverse health and safety outcomes have been reported and present on-going challenges for communities. Scientists, health-care professionals, and treatment providers have quickly mobilized to better understand and treat the outcomes.

The five substances the Department has recommended for addition to the sentencing guidelines belong to two drug classes: synthetic cathinones and synthetic cannabinoids, based on their respective structure and/or effect. Mephedrone, methylone, and MDPV are synthetic cathinones, while JWH-018 and AM-2201 are synthetic cannabinoids. All five substances are schedule I controlled substances as a result of legislation or DEA regulation.[1] Schedule I substances are substances with a high potential for abuse and no approved medical use. Further, they have no industrial use and were introduced on the designer drug market and abused for their psychoactive properties. As a result of trafficking and abuse, four of the five substances were emergency (temporarily) controlled by the Drug Enforcement Administration (DEA) in 2011

[1] See 76 Fed. Reg. 65371 (Oct. 21, 2011); and Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144,126 Stat. 993 (2012).

upon the finding they posed an imminent hazard to public safety.[2] As they continued to appear on the illicit market, researchers continued to collect information to investigate the neurobiological and psychological correlates and risk factors associated with their misuse. As would be expected, there are no published studies in the scientific literature suggesting any beneficial effects or therapeutic value for the individual. The DEA, in collaboration with the National Institute on Drug Abuse, initiated pharmacological studies on NPS, including these five substances, to collect additional information and further characterize and compare them with known drugs of abuse. Based on these studies and the information published in the scientific literature, direct comparisons can be made to substances currently listed under the federal sentencing guidelines. Further, MDMA continues to be encountered in investigations, and NPS mimics for MDMA are a recent development in the illicit market.

Trafficking Findings and Patterns

Synthetic cannabinoids, such as JWH-018 and AM-2201, and cathinones, such as MDMA and methylone, are almost entirely manufactured in China. They are then typically imported into the United States through mail services. Once in the United States, the bulk shipments are most often packaged into individual saleable units – or mixed with organic leaves and then packaged. Prior to being placed in Schedule I, they were distributed for sale at gas stations, convenience stores and head shops or sold directly to individuals via the Internet. They were sold in packages adorned with bright colors and cartoons to attract younger users, and they were often marketed using flavors such as blueberry, strawberry, mango, and bubblegum. Since being scheduled, the market for these drugs has gone underground and now resembles the market for other illegal drugs.

Unfortunately, when DEA initiates temporary control of a synthetic designer drug like these using statutory or administrative procedures, those who traffic them will often alter the chemical composition of the drugs slightly, and in doing so create a different chemical structure not specifically identified in the controlling statutes or regulations. Despite the alterations, these new chemical compounds remain just as potent and just as harmful.

Large profits can be made selling synthetic cannabinoids and cathinones, driving the wholesale and retail distribution of these products. Information DEA has obtained through its investigations show that a $1,500 purchase of a bulk synthetic drug from China can generate as much as $250,000 of revenue at the retail level. It is clear that the income generated from distributing these products is, and will continue to be, a driving factor for manufacturers, distributors, and retailers to seek and find substitute products that are not yet controlled or banned by federal or state law and thus stay one step ahead of enforcement authorities.

According to the National Forensic Laboratory Information System (NFLIS), seizures of synthetic cannabinoids by federal, state, and local forensic laboratories increased from 23 reports in 2009 to 32,784 reports in 2013. Seizures of synthetic cathinones increased from 29 reports in 2009 to 15,673 reports in 2013.

[2] See 76 Fed. Reg. 65371 (Oct. 21, 2011).

Synthetic Cathinones

Synthetic cathinones are a class of β-ketoamphetamine substances that emerged as NPS and are known for their hallucinogenic and psychostimulant properties, as well as for their abuse and toxicity. Synthetic cathinones are structurally and pharmacologically similar to amphetamine, methylenedioxymethamphetamine (MDMA), and cathinone. Synthetic cathinones produce their effects via the release or reuptake of various neurotransmitters including dopamine, norepinephrine, and/or serotonin.[3] Studies suggest that cathinones have high blood-brain barrier permeability.[4] The onset of drug effects is rapid with the side effects lasting from hours to days. Since their introduction into the illicit drug market, synthetic cathinones have been implicated by coroners' offices in the death of many individuals.[5]

Methylone, mephedrone, and MDPV are synthetic cathinones that have many similarities with the Schedule I substances cathinone, methcathinone, and MDMA, and the Schedule II stimulants amphetamine, methamphetamine, and cocaine. The clinical presentation of intoxication from these three substances is like that seen with MDMA and other substances (*e.g.*, cathinone, methcathinone, MDMA, amphetamine, methamphetamine, and cocaine) that have a stimulant effect on the central nervous system. Adverse effects associated with the consumption of methylone, mephedrone and MDPV include palpitations, hyperthermia, seizures, hyponatremia, bruxism, sweating, hypertension, tachycardia, headache, thirst, mydriasis, tremor, fever, confusion, psychosis, paranoia, hallucinations, combativeness, agitation, and death.[6]

The DEA has encountered these synthetic cathinones being trafficked for their psychoactive properties. These substances are falsely marketed as "research chemicals," "plant food or fertilizer," "jewelry cleaner," "stain remover," "insect repellant," or "bath salts." Prior to being regulated, they were sold at smoke shops, head shops, convenience stores, adult book stores, gas stations, and on the Internet, with packaging that contains the warning "not for human consumption." In addition, methylone, mephedrone, and MDPV at one time were promoted as

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[3] RA Gregg & SM Raws. *Behavioral Pharmacology of Designer Cathinones: A Review of the Preclinical Literature*, 97.1 LIFE SCI. 27, 27-30 (2014).

[4] LD Simmler et al., *Pharmacological Characteriztion of Designer Cathinones In Vitro*, 168.2 BRIT. J. PHARMACOLOGY 458, 458-470 (2013).

[5] LJ Marinetti & HM Antonicides. *Analysis of Synthetic Cathinones Commonly Found in Bath Salts in Human Performance and Postmortem Toxicology: Method Development, Drug Distribution, and Interpretation of Results*, 137 J. ANALYTICAL TOXICOLOGY 135, 135-146 (2013); JF Wyman et al., *Postmortem Tissue Distribution of MDPV Following Lethal Intoxication by "Bath Salts"*, 37.3 J. ANALYTICAL TOXICOLOGY 182, 182-185 (2013); SJ deRoux & WA Dunn, *"Bath Salts" the New York City Medical Examiner Experience: A 3-Year Retrospective Review* J. FORENSIC SCI., ahead of print; TH Wright et al., *Deaths Involving Methylenedioxypyrovalerone (MDPV) in Upper East Tennessee*, 58.6 J. FORENSIC SCI. 1558, 1558-1562 (2013); PN Carbone et al., *Sudden Cardiac Death Associated with Methylone Use*, 34.1 AM. J. FORENSIC MED. AND PATHOLOGY 26, 26-28 (2013).

[6] JM Pearson et al., *Three Fatal Intoxications Due to Methylone*, 36 J. ANALYTICAL TOXICOLOGY 444, 444-451 (2012); B. Warrick et al., *Lethal Serotonin Syndrome After Methylone and Butylone Ingestion*, 8 J. MED. TOXICOLOGY 65, 65-68 (2012); B. Cawrse et al., *Distribution of Methylone in Four Postmortem Cases*, 36 J. ANALYTICAL TOXICOLOGY 434, 434-439 (2012); J. Wyman et al., *Postmortem Tissue Distribution of MDPV Following Lethal Intoxication by "Bath Salts*," 37 J. ANALYTICAL TOXICOLOGY 182, 182-185 (2013); B. Murray *et al.*, *Death Following Recreational Use Of Designer Drug "Bath Salts" Containing 3,4-Methylenedioxypyrovalerone (MDPV)*, 8 J. MED. TOXICOLOGY 69, 69-75 (2012); K. Kesha et al., *Methylenedioxypyrovalerone ("Bath Salts"), Related Death: Case Report And Review Of The Literature*, 58 J. FORENSIC SCI. 1654, 1654-1659 (2013).

being "legal" alternatives to cocaine, methamphetamine, and MDMA, because at that time detection of these substances was not included in the routine drug screen for illicit substances.

On October 21, 2011, the Administrator of the DEA published a Final Order in the Federal Register temporarily placing methylone, mephedrone and MDPV into Schedule I of the CSA upon finding that these substances pose an imminent threat to public safety.[7] On July 9, 2012, President Obama signed the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) (FDASIA), which amended several provisions of the CSA. In particular, the FDASIA amended Schedule I of section 202(c) of the CSA to include the synthetic cathinones mephedrone and MDPV. Methylone was permanently controlled via the administrative scheduling process on April 12, 2013.[8]

Methylone

Research in anti-depressant and anti-Parkinson agents resulted in the development and patenting of methylone in 1996.[9] However, there is no evidence that methylone has a legitimate non-research use and, according to the Department of Health and Human Services (HHS), there are no approved drug products or new drug applications that contain methylone. Evidence indicates that methylone is abused by individuals for its psychoactive effects. Desired effects reported by abusers of synthetic cathinones substances include euphoria, increased sociability, energy, empathy, increased alertness, and improved concentration and focus.

Scientific Evidence of the Substance's Pharmacological Effect

Studies indicate that methylone is more similar in its pharmacological effects to MDMA than to methamphetamine or amphetamine. In microdialysis studies, methylone produces elevations in the dialysates dopamine and serotonin (5-HT) with a preferential increase in 5-HT, which are qualitatively analogous to the effects of MDMA but less potent.[10] In contrast, methamphetamine causes preferential increase in dialysate dopamine rather than serotonin. These selective effects on the neurotransmitters (dopamine and serotonin) are relevant properties of the substances. They show that methylone is a weak psychomotor stimulant compared to methamphetamine. Whereas methamphetamine elicits a sustained increase in horizontal locomotor activity, methylone produces a transient increase in locomotor activity. However, in a study by Lopez-Annau (2012), methylone, compared to MDMA, had similar effects on locomotor activity.[11]

Studies indicate that methylone, like MDMA, produces pharmacological effects that are similar to those of substances that cause a stimulant effect on the central nervous system. The drug discrimination paradigm is used as an animal model of human subjective effects. This procedure provides a direct measure of stimulus specificity of a test drug in comparison with a

[7] 76 Fed. Reg. 65371 (Oct. 21, 2011).
[8] 78 Fed. Reg. 21818 (Apr. 12, 2013).
[9] P Jacob and A Shulgin, U.S. Patent No. WO 1996039122 (filed Jun. 6, 1996).
[10] MH Baumann et al., *The Designer Methcathinone Analogs, Mephedrone and Methylone, are Substrates for Monoamine Transporters*, 37 NEUROPSYCHOPHARMACOLOGY 1192, 1192-1203 (2012).
[11] R Lopez-Arnau et al., *Comparative Neuropharmacology Of Three Psychostimulant Cathinone Derivatives: Butylone, Mephedrone and Methylone*. 167.2 BRIT. J. PHARMACOLOGY 407, 407-420 (2012).

known standard drug, or a neutral stimulus (*e.g.* injection of saline water). In the drug discrimination paradigm, if a new drug or substance has discriminative stimulus effects in animals similar to a known drug of abuse, it is highly likely that this new drug will produce pharmacological effects (including subjective effects) in humans that would be qualitatively and quantitatively similar to the known drug of abuse and would be similarly abused by humans.[12] Data from a published drug discrimination study indicates that methylone (ED_{50} = 1.60 mg/kg) fully substitutes for the discriminative stimulus effects produced by MDMA (ED_{50}=0.76 mg /kg) in rats.[13] Similarly, data from another published drug discrimination study also indicate that methylone (ED_{50} = 2.66 mg/kg) fully substitutes for the discriminative stimulus effects produced by methamphetamine.[14] MDMA (ED_{50} = 1.83 mg/kg), which was previously tested by these authors, also fully substitutes for the discriminative stimulus effects produced by methamphetamine.[15] Based on these studies, methylone is approximately half as potent as MDMA in these drug discrimination studies.

The Substance's History and Current Pattern of Abuse

DEA forensic laboratories have analyzed drug exhibits received from state, local, or federal law enforcement agencies that were found to contain methylone. Methylone, like MDMA, is commonly encountered in powder, capsule, and tablet form. Information from published scientific studies indicate that the most common routes of administration for methylone are by swallowing capsules or tablets or by snorting the powder. The reported average amount of use reported for methylone ranged from 100 mg to 250 mg.[16] In contrast, the average amount of MDMA used ranged from 75 mg to 125 mg.[17] Evidence from poison centers, published case reports, and law enforcement encounters suggest that the main users of methylone are young adults. There is evidence that methylone may be co-ingested with other substances including other synthetic cathinones, pharmaceutical agents, or other recreational substances. In fact, some products that were sold as MDMA (marketed as "Molly") were found to contain methylone.

[12] JB Kamien et al., *Drug Discrimination by Humans Compared to Nonhumans: Current Status and Future Directions*, 111.3 PSYCHOPHARMACOLOGY 259, 259-270 (1993); RL Balster & GE Bigelow, *Guidelines and Methodological Reviews Concerning Drug Abuse Liability Assessment*, 70.3 DRUG AND ALCOHOL DEPENDENCE Suppl, S13, S13-S40 (2003); LV Panlilio & SR Goldberg, *Self-Administration of Drugs in Animal and Humans as a Model and an Investigative Tool*, 102.12 ADDICTION 1863, 1863-1870 (2007).

[13] TA Dal Cason et al., *Cathinone: an Investigative of Several N-Alkyl and Methylenedioxy-substituted Analogs*, 58.4 PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR 1109, 1109-1116 (1997).

[14] MB Gatch et al., *Locomotor Stimulant and Discriminative Stimulus Effects of 'Bath Salt' Cathinone*,24.5-24.6BEHAVIORAL PHARMACOLOGY 437, 437-447 (2013).

[15] National Institute on Drug Abuse email communication (2012).

[16] JP Kelly et al., *Cathinone Derivatives: a Review of Their Chemistry, Pharmacology, Toxicology*, 7-8 DRUG TESTING AND ANALYSIS 439, 439-453 (2011).

[17] J Cami et al, *Human Pharmacology of 3,4-Methylenedioxymethamphetamine ("Ecstasy"): Psychomotor, Performance and Subjective Effects*, 20.4 J. CLINICAL PSYCHOPHARMACOLOGY, 455, 455-466 (2000); AC Parrott, *Human Psychobiology of MDMA or 'Ecstasy': an Overview of 25 Years of Empirical research*, 28.4 HUMAN PSYCHOPHARMACOLOGY, 289, 289-307 (2013).

The Scope, Duration and Significance of Abuse

According to forensic laboratory data as reported by the National Forensic Information Laboratory System (NFLIS),[18, 19] law enforcement began encountering methylone in February 2009. Through January 2017, NFLIS has reported 21,839 law enforcement encounters involving methylone.[20] Additionally, the U.S. Customs and Border Protection (CBP) has seized large quantities of methylone during this same period.

Risk to Public Health

Methylone has been reported to cause a number of stimulant-like adverse effects. The clinical presentation of intoxication from methylone is similar to that seen with MDMA and other substances that have a stimulant effect on the central nervous system (*e.g.*, cathinone, methcathinone, MDMA, amphetamine, methamphetamine, and cocaine). Adverse effects associated with the consumption of methylone include palpitations, hyperthermia, seizures, hyponatremia, bruxism, sweating, hypertension, tachycardia, headache, thirst, mydriasis, tremor, fever, confusion, psychosis, paranoia, hallucinations, combativeness, agitation, and death. Some published case reports describing adverse effects of methylone are summarized below.

- A study by Pearson reported on a 19-year-old female who took a pill known as "Molly" collapsed and recovered then complained of not feeling well.[21] Thereafter, she developed seizures. Emergency personnel were called and the female was transported to the hospital. At the hospital she suffered cardiac complications and later died. Toxicology tests identified methylone in specimens from the decedent. No other recreational substances were detected. The medical examiner concluded that the cause of death was methylone intoxication.

- The Pearson study also described the death of a 23-year-old male.[22] The decedent was witnessed to take what was thought to be LSD at a club. The decedent was acting erratically and irrationally and so the decedent was removed from the club and placed in the back of a van by securing the decedent to a chair using saran wrap. Sometime later, the decedent was found having seizures. Emergency personnel were called and the decedent was transported to the hospital. The decedent had hyperthermia and cardiac

[18] The NFLIS is a program of the DEA, Diversion Control Division. NFLIS systematically collects drug identification results and associated information from drug cases submitted to and analyzed by Federal, State and local forensic laboratories. NFLIS represents an important resource in monitoring illicit drug abuse and trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS is a comprehensive information system that includes data from forensic laboratories that handle approximately 98% of an estimated nearly 1.0 million distinct annual State and local drug analysis cases. NFLIS includes drug chemistry results from completed analyses only.

[19] While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 Fed. Reg. 77330, 77332 (Dec. 12, 2011).

[20] Query date February 27, 2017, Federal, State, and local laboratories.

[21] JM Pearson et al., *Three Fatal Intoxications Due to Methylone*, 36.6 J. ANALYTICAL TOXICOLOGY 444, 444-451 (2012).

[22] *Id.*

complications. The decedent died 45 minutes after his arrival at the hospital. The medical examiner listed the cause of death as intoxication by methylone.

- Another incident reported by Pearson involved the death of a 23-year-old male initially suspected of using methylone.[23] The decedent was walking in and out of traffic and acting belligerently. The decedent was detained by law enforcement and transported to the hospital. The decedent had a high temperature and subsequently went into respiratory failure. After several attempts by medical personnel to stabilize the decedent, he died. Toxicology testing identified methylone in specimens from this individual. The medical examiner listed the cause of death as intoxication by methylone.

- Warrick *et al.* described the death of a 24-year-old female who ingested two capsules of what was thought to be "Ecstasy" at a concert.[24] After being found unconscious by emergency personnel, the decedent was taken to the emergency department. The comatose patient suffered from hyperthermia, tachycardia, mydriasis, tachypnea and some tremors and later died. Toxicology tests identified methylone and butylone in specimens from this individual. Laboratory analysis also identified methylone and butylone in the powder obtained from a capsule that was found on the decedent. The cause of death mentioned by the medical examiner was serotonin syndrome secondary to methylone and butylone intoxication.

- Cawrse *et al.* described the death of a 19-year-old male.[25] The decedent died while performing a physical fitness assessment. Toxicology tests identified methylone in specimens from this individual. The cause of death was cardiac arrest associated with methylone.

- The death of a 39-year-old male was reported by Wyman *et al.*[26] Family members indicated that the male, who had a history of schizophrenia, depression, and drug abuse, had been snorting "bath salts." The subject was found dead in his bed. Empty jars of "bath salts" ("TranQuility" and "Infinity") and synthetic cannabinoids ("Demon" and "Flame") were found in the trash. A toxicological screen detected MDPV in multiple tissues, urine and blood samples from the decedent. Other substances detected were nicotine, cotinine, pseudoephedrine, m-chlorophenylpiperazine and methylone. The cause of death was acute MDPV intoxication.

- Kovacs *et al.* described the case of a 16-year-old male who lost consciousness at a party.[27] The decedent died of sudden cardiac death at the hospital after attempts to save his life were unsuccessful. The decedent suffered from cardiac malformation and

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[23] *Id.*
[24] BJ Warrick et al., *Lethal Serotonin Syndrome after Methylone and Butylone Ingestion*, 8.1 J. MED. TOXICOLOGY 65, 65-68 (2012).
[25] BM Cawrse et al., *Distribution of Methylone in Four Postmortem Cases*, 36.6 J. ANALYTICAL TOXICOLOGY 434, 434-439 (2012).
[26] JF Wyman et al., *Postmortem Tissue Distribution of MDPV Following Lethal Intoxication by "Bath Salts"*.,37 J. ANALYTICAL TOXICOLOGY 182, 182-185 (2013).
[27] K Kovacs et al., *A New Designer Drug: Methylone Related Death*. 157.7 ORV HETIL 271, 271-276 (2012).

bronchial asthma. The toxicology testing identified methylone in the specimens from this individual. The authors concluded that the predisposing factors along with methylone may have resulted in the sudden cardiac death of this individual.

- A 22-year-old female developed rhabdomyolysis after ingesting "legal ecstasy" which was analyzed to be a mixture of methylone and ethcathinone.[28] She also suffered from recurrent seizures, severe hyponatremia (abnormally low concentration of sodium in the blood), nystagmus (involuntary rapid eye movement), hyperreflexia, and bruxism. All her symptoms resolved after treatment that required hospitalization.

- Katagi *et al.* reported two cases of acute toxicity from the confirmed ingestion of methylone.[29] A 19-year-old male was taken to the emergency department suffering from dementia after ingesting an unknown amount of methylone powder. In the second case, a 29-year-old male was taken to the emergency department suffering from acute toxicity after taking an unknown amount of a mixture of methylone and a hallucinogen.

- A 19-year-old female with a history of illicit drug use was found 100 yards from the beach. High blood and liver concentrations of methylone were found with THC. The cause of death was certified as drowning due to acute methylone intoxication and the manner of death was certified as accidental.[30]

- A 19-year-old male collapsed while jogging and died.[31] He had no significant health issues. A toxicology report confirmed the presence of methylone but found no other substances including synthetic cathinones (4-FMC, mephedrone, ethylone, butylone, MDPV, and naphyrone).

- A 21-year-old male who ingested cannabis and methylone died.[32] After ingesting the substances he had difficulty breathing. Emergency medical services were called and found the individual in cardiopulmonary arrest. An autopsy report concluded that death was due to respiratory distress that may have been provoked by the absorption of toxic substances. An analysis of biological specimens from the decedent identified methylone and cannabinoids. Other routine drugs of abuse were not detected.

Mephedrone

Mephedrone, also known as "m-cat," "Meow," and "mad cow," is a psychoactive synthetic cathinone that is structurally and pharmacologically similar to the Schedule I and II substances cathinone, methcathinone, MDMA, and methamphetamine. There is no evidence that

[28] C Boulanger-Gobeil *et al.*, *Seizures and Hyponatremia Related to Ethcathinone and Methylone Poisoning*, 8 J. MED. TOXICOLOGY 59, 59-61 (2011).
[29] L Katagi et al., *Metabolism and Forensic Toxicology Analysis of the Extensively Abused Designer Drug Methylone*, 40 TIAFT BULLETIN 30, 30-35(2010).
[30] IM McIntyre et al., *Acute Methylone Intoxication in an Accidental drowning – A Case Report*, 231 FORENSIC SCI. INT'L e1, e1-e3 (2013),
[31] P Carbone et al., *Sudden Cardiac Death Associated with Methylone Use, 34.1* AM J. FORENSIC MED. AND PATHOLOGY,26, 26-28 (2013).
[32] L Barrios et al., *Death Following Ingestion of Methylone*, 30.2 INL'T J. LEGAL MED. 381, 381-385. (2016).

mephedrone has a legitimate non-research use, and according to HHS, there are no approved drug products or new drug applications that contain mephedrone. Evidence indicates that mephedrone is being abused by individuals for its psychoactive effects. Desired effects reported by abusers of synthetic cathinone substances include euphoria, increased sociability, energy, empathy, increased alertness, and improved concentration and focus.

Scientific Evidence of the Substance's Pharmacologic Effect

To date, there is one human study evaluating the efficacy and potency of mephedrone relative to MDMA. Data that was presented at the 77th Annual Scientific Meeting of the College on Problems of Drug Dependence described the abuse liability of mephedrone in humans compared to MDMA.[33] In this small clinical study (12 healthy males who used psychostimulants recreationally), 200 mg of mephedrone was found to be similar to MDMA (100 mg) in somatic (*i.e.,* blood pressure, heart rate and temperature) and subjective effects (visual analog scales –VAS, ARCI-49 short form and VESSPA questionnaire). Based on this study, mephedrone has a stimulant effect that is similar to MDMA but less potent. However, these conclusions are made with the limitations since the number or participants were small and only one dose of mephedrone was evaluated.

Studies indicate that mephedrone is more similar in its pharmacological effects to MDMA than to methamphetamine or amphetamine.[34] In microdialysis studies, mephedrone produces elevations in the dialysates dopamine and serotonin (with preferential effects on serotonin), which are qualitatively analogous to the effects of MDMA but less potent.[35] In contrast, methamphetamine causes preferential increase in the dialysate dopamine rather than serotonin. Studies also show that mephedrone is a weak psychomotor stimulant compared to methamphetamine. Whereas methamphetamine elicits a sustained increase in horizontal locomotor activity, mephedrone produces a transient increase in locomotor activity. Data from other studies support the comparison of mephedrone to MDMA. The neurochemical and functional properties of mephedrone resemble those of MDMA as demonstrated in another microdialysis study.[36] In an additional study that claims MDMA-like drugs can be discerned

[33] M Farre et al., *A Comparison of the Clinical Abuse Liability of MDMA and Mephedrone*, 37.8 CLINICAL THERAPEUTICS e130 (2015).
[34] J Kehr et al., *Mephedrone, Compared with MDMA (Ecstasy) and Amphetamine, Rapidly, Increases Both Dopamine and 5-HT Levels in Nucleus Accumbens of Awake Rats*, 164.8 BRIT. J. PHARMACOLOGY 1949, 1949-1958 (2011); MH Baumann et al., *The Designer Methcathinone Analogs, Mephedrone and Methylone, are Substrates for Monoamine Transporters*, 37 NEUROPSYCHOPHARMACOLOGY 1192, 1192-1203 (2012); P-K Huang et al., *Contrasting Effects of d-Methamphetamine,3,4-Methylenedioxymethamphetamine, 3,4-Methylenedioxypyrovalerone, and 4-Methylmethcathinone on Wheel Activity in Rats*, 126.1-126.2 DRUG AND ALCOHOL DEPENDENCE 168, 168-175 (2012).
[35] MH Baumann et al., *The Designer Methcathinone Analogs, Mephedrone and Methylone, are Substrates for Monoamine Transporters*, 37 NEUROPSYCHOPHARMACOLOGY1192, 1192-1203 (2012).
[36] J Kehr et al., *Mephedrone, Compared with MDMA (Ecstasy) and Amphetamine, Rapidly, Increases Both Dopamine and 5-HT Levels in Nucleus Accumbens of Awake Rats*, 164.8 BRIT. J. PHARMACOLOGY 1949, 1949-1958 (2011).

from methamphetamine-like drugs by measuring a specific locomotor activity (voluntary wheel activity), mephedrone is more similar to MDMA than to MDPV or methamphetamine.[37]

In support of the clinical study mentioned earlier, data from drug discrimination studies in rats indicate that mephedrone, like MDMA, produces pharmacological effects that are similar to those of substances that cause a stimulant effect on the central nervous system. The drug discrimination paradigm is used as an animal model of human subjective effects. This procedure provides a direct measure of stimulus specificity of a test drug in comparison with a known standard drug, or a neutral stimulus (*e.g.* injection of saline water). In the drug discrimination paradigm, if a new drug or substance has discriminative stimulus effects in animals similar to a known drug of abuse, it is highly likely that this new drug will produce pharmacological effects (including subjective effects) in humans that would be qualitatively and quantitatively similar to the known drug of abuse and would be similarly abused by humans.[38] Data from a published drug discrimination study indicate that MDMA fully substitutes for the discriminative stimulus effects produced by mephedrone (ED_{50}=0.90 mg/kg) in rats.[39] The potency values were not stated in the article but the ranked order of potency as determined from the figure is: methamphetamine ≥ mephedrone > MDMA > cocaine. Thus, mephedrone is substantially similar to MDMA in pharmacological effect but more potent than MDMA in this assay.

The Substance's History and Current Pattern of Abuse

DEA forensic laboratories have analyzed drug exhibits received from state, local, or federal law enforcement agencies that were found to contain mephedrone. Mephedrone, like MDMA, is commonly encountered in the form of powders, capsules, and tablets. Information from published scientific studies indicate that the most common routes of administration for methylone are ingestion by swallowing capsules or tablets or nasal insufflation by snorting the powder. The reported average amount of use of mephedrone ranged from 0.5 to 4 grams depending on the route of administration and the number of doses taken. According to self-reported drug users, the amounts for snorting mephedrone ranged from 5 to 75 milligrams whereas for oral administration it ranged from 150 to 250 milligrams.[40] It has also been reported that mephedrone is used in binges. Abusers have reported that typical sessions using mephedrone have last approximately 10.4 hours with some individuals administering several times throughout a session. A possible reason for binging may be to prolong the duration of effects. The average amount of MDMA used ranged from 75 mg to 125 mg (oral

[37] P-K Huang et al., *Contrasting Effects of d-Methamphetamine,3,4-Methylenedioxymethamphetamine, 3,4-Methylenedioxypyrovalerone, and 4-Methylmethcathinone on Wheel Activity in Rats*, 126.1-126.2 DRUG AND ALCOHOL DEPENDENCE 168, 168-175 (2012).
[38] JB Kamien et al., *Drug Discrimination by Humans Compared to Nonhumans: Current Status and Future Directions*, 111.3 PSYCHOPHARMACOLOGY 259, 259-270 (1993); RL Balster & GE Bigelow, *Guidelines and Methodological Reviews Concerning Drug Abuse Liability Assessment*, 70.3 DRUG AND ALCOHOL DEPENDENCESuppl, S13, S13-S40 (2003); LV Panlilio & SR Goldberg, *Self-Administration of Drugs in Animal and Humans as a Model and an Investigative Tool*, 102.12 ADDICTION, 1863, 1863-1870 (2007).
[39] KJ Varner et al., *Comparison of the Behavioral and Cardiovascular Effects of Mephedrone with Other Drugs of Abuse in Rats*, 225.3 PSYCHOPHARMACOLOGY 675, 675-685 (2013).
[40] JP Kelly et al., *Cathinone Derivatives: a Review of Their Chemistry, Pharmacology, Toxicology*, 7-8 DRUG TESTING AND ANALYSIS 439, 439-453 (2011).

administration).[41] Evidence from poison centers, published case reports, and law enforcement encounters suggest that the main users of mephedrone are young adults. There is evidence that mephedrone may be co-ingested with other substances including other synthetic cathinones, pharmaceutical agents, or other recreational substances.

Users from drug surveys reported that mephedrone, like methylone, MDPV, and other synthetic cathinones, has an effect profile similar to known drugs of abuse like cocaine and MDMA. The desired psychoactive effects reported by users include euphoria, general stimulation, empathy, enhanced music appreciation, hallucinations, increased insight, elevated mood, decreased hostility, improved mental function, and mild sexual stimulation.[42] Participants in a survey of readers of a popular UK dance music magazine reported that mephedrone gave a better high than cocaine. Another survey that was advertised on websites frequented by drug users found that users considered the effects of mephedrone to be similar to those of MDMA. This is consistent with studies in animals that demonstrated that methylone resembles MDMA in its behavioral profile. As explained above, some products that were sold as MDMA (marketed as "Molly") actually contained methylone; other products were found to contain mephedrone.

The Scope, Duration and Significance of Abuse

According to forensic laboratory data as reported by the National Forensic Information Laboratory System (NFLIS), mephedrone started to be encountered by law enforcement in April 2009. Through January 2017, NFLIS has reported 716 law enforcement encounters involving mephedrone (query date February 27, 2017, Federal, State, and local laboratories). Additionally, seizures of mephedrone have occurred by the U.S. Customs and Border Protection (CBP).

Risk to Public Health

Mephedrone has been reported to cause a number of stimulant-like adverse effects. The clinical presentation of intoxication from mephedrone is similar to MDMA and other substances that have a stimulant effect on the central nervous system (*e.g.*, cathinone, methcathinone, MDMA, amphetamine, methamphetamine, and cocaine). Adverse effects associated with the consumption of mephedrone include palpitations, hyperthermia, seizures, hyponatremia, bruxism, sweating, hypertension, tachycardia, headache, thirst, mydriasis, tremor, fever, confusion, psychosis, paranoia, hallucinations, combativeness, agitation, and death. Published case reports describing mephedrone related adverse effects are summarized below.

- A 22-year-old male was found unresponsive at his home. He was transported to the hospital where he died. An autopsy revealed heroin and high concentrations of mephedrone. Multiple drug toxicity associated with mephedrone and heroin use was reported as the cause of death.[43]

[41] AC Parrott, *Human Psychobiology of MDMA or 'Ecstasy': an Overview of 25 Years of Empirical Research*, 28.4 HUMAN PSYCHOPHARMACOLOGY 289, 289-307 (2013).
[42] 76 FR 65371.
[43] AJ Dickson et al., *Multiple-drug Toxicity Caused by Coadministration of 4-Methylmethcathinone (Mephedrone) and Heroin*, 34.3 J. ANALYTICAL CHEMISTRY 162, 162-166 (2010).

- A 49-year-old female died after snorting approximately 0.5g of mephedrone that she purchased from the Internet. She also consumed alcohol and smoked marijuana. A few hours after taking mephedrone, she complained of a sore chest, vomited, and then collapsed. She was transported to the hospital by emergency services but died despite efforts to resuscitate her. A medical examiner attributed this death to the adverse effects of mephedrone.[44]

- A 19-year-old male died after taking an unknown amount of mephedrone along with alcohol, and MDMA at a party. Others at the party described the 19-year-old as being sweaty and acting strangely and subsequently he collapsed. Emergency services were called and he was taken to the hospital but efforts to resuscitate him were unsuccessful. A medical examiner found mephedrone to be the principal cause of death.[32]

- A 55-year-old female was found dead in bed. Her death was attributed to the combined effects of mephedrone and methadone.[32]

- A 17-year-old male died from injuries sustained in a vehicular collision. While driving on the wrong side of the road he collided head-on with an oncoming car. Mephedrone was detected in his blood and is suspected to have affected the ability of this individual to drive.[32]

- A 36-year-old man died from substantial blood loss that may have led to aggravated heart and blood pressure problems after he was arrested by police for extreme agitation.[45] Mephedrone was identified in the tablets found in the house of the deceased. Toxicological analyses of the post-mortem samples from the decedent detected mephedrone, cocaine, MDMA, oxazepam, midazolam.

- An approximately 30-year-old man was found in a critical state in a staircase. Efforts to save him were unsuccessful. Authors concluded that death was due to fatal mephedrone intoxication.[46]

- Acute mephedrone-related toxicity was analytically confirmed in seven male patients. The most common symptom/sign reported was agitation. Other symptoms/signs included palpitations, chest pain, seizures, headaches (acute sympathomimetic toxidrome).[47]

- Nicholson *et al*. described a case involving a 19-year-old man who presented to the emergency room with central crushing chest pain.[48] Clinical tests showed myocardial

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[44] PD Maskell et al., *Mephedrone (4-Methylmethcathinone)-related Deaths*, 35.3 J. ANALYTICAL CHEMISTRY 189, 189-191 (2011).
[45] KJ Lusthof et al., *A Case of Extreme Agitation and Death after the Use of Mephedrone in The Netherlands*, 206.1-206.3 FORENSIC SCI. INT'L e93, e93-e95 (2011).
[46] P Adamowicz et al., *Fatal Mephedrone Intoxication – A Case Report*, 37.1 J. ANALYTICAL TOXICOLOGY 37, 37-42 (2013).
[47] DM Wood et al., *Recreational Use of Mephedrone (4-Methylmethcathinone, 4-MMC) with Associated Sypathomimetic Toxicity*,.6.3 J. MED. TOXICOLOGY 327, 327-330 (2010).
[48] PJ Nicholson et al., *Headshop Heartache: Acute Mephedrone 'Meow' Myocarditis*, 96.24 HEART 2051, 2051-2052 (2010).

inflammation. He admitted to ingesting plant food that contained mephedrone. Toxicology screening of biological samples confirmed the presence of mephedrone. No other neurostimulant drugs were detected. He was successfully treated and discharged five days after his admission.

- Debruyne *et al.* reported that seven cases in France related to the use of mephedrone were reported to the Center of Evaluation and Information on Pharmacodependence (Addictovigilance).[49] In one case, a young man was involved in a vehicular accident after snorting mephedrone. His blood tested positive for mephedrone. In another case, an individual used mephedrone in place of cocaine.

- Wood *et al.* reported a case of acute toxicity in the United Kingdom after the abuse of mephedrone.[50] A 22-year-old male presented to the emergency room with sympathomimetic toxicity after ingesting 200 milligrams of mephedrone. He developed palpitation, blurred vision, mydriasis, agitation, tachycardia, and an elevated body temperature. His symptoms resolved after treatment. Mephedrone was the only substance detected in his serum.

- Torrance and Cooper reported the death of four individuals whose blood samples tested positive for mephedrone.[51] These fatalities were not attributed to the sole use of mephedrone but they can be considered to be evidence of the misuse of mephedrone and the subsequent harm they may cause to the user or general public.

Methylenedioxypyrovalerone

Methylenedioxypyrovalerone (MDPV) is closely related in structure to phenethylamines such as the Schedule I and II substances methamphetamine, cathinone, methcathinone, and methylenedioxymethamphetamine (MDMA). MDPV is also structurally related to pyrovalerone, which is a psychoactive drug that was used to treat chronic lethargy and fatigue. There is no evidence that MDPV has a legitimate non-research use, and according to HHS, there are no approved drug products or new drug applications that contain MDPV. MDPV and other cathinone derivatives (including those which bear ring-group substituents) have been reported to induce subjective effects similar to those induced by stimulant drugs of abuse such as cocaine, amphetamine, MDMA, and methcathinone. Indeed, evidence indicates that MDPV is being abused by individuals for its psychoactive effects. Desired effects reported by abusers of synthetic cathinone substances include euphoria, increased sociability, energy, empathy, increased alertness, and improved concentration and focus.

Scientific Evidence of the Drug's Pharmacological Effects

[49] D Debruyne et al., *Mephedrone: a Designer Drug of recent Use in France*, 65.6 THERAPIE 519, 519-524(2010).
[50] DM Wood et al., *Recreational Use of Mephedrone (4-Methylmethcatinone, 4-MMC) with Associated Sympathomimetic Toxicity*, 6.3 J. MED. TOXICOLOGY 327, 327-330 (2010).
[51] H Torrance & G Cooper, *The Detection of Mephedrone (4-Methylmethcathinone) in 4 Fatalities in Scotland*, 202.1-202.3 FORENSIC SCI. INT'L E62, e62-e63 (2010).

In a study that claims MDMA-like drugs can be discerned from methamphetamine-like drugs by measuring a specific locomotor activity (voluntary wheel activity), MDPV is more similar to methamphetamine than to MDMA.[52] In addition, MDPV is a powerful locomotor stimulant like methamphetamine.[53]

Drug discrimination studies indicate that MDPV produces pharmacological effects that are similar to those of methamphetamine and cocaine. As described above, the drug discrimination paradigm is used as an animal model of human subjective effects. This procedure provides a direct measure of stimulus specificity of a test drug in comparison with a known standard drug, or a neutral stimulus (*e.g*. injection of saline water). In the drug discrimination paradigm, if a new drug or substance has discriminative stimulus effects in animals similar to a known drug of abuse, it is highly likely that this new drug will produce pharmacological effects (including subjective effects) in humans that are qualitatively and quantitatively similar to the known drug of abuse and would be similarly abused by humans.[54] Data from a published drug discrimination study indicate that MDPV (ED_{50} = 0.67 mg/kg) fully substitutes for the discriminative stimulus effects produced by methamphetamine (ED_{50} = 0.37 mg/kg) in rats.[55] Data from another published drug discrimination study indicate that MDPV (ED_{50} = 0.03 mg/kg) fully substitutes for the discriminative stimulus effects produced by methamphetamine (ED_{50} = 0.08 mg/kg) in mice.[56] Based on these drug discrimination studies, MDPV is at least as potent if not more potent than methamphetamine. The self-administration study is another behavioral study done in rodents that has been used to predict the abuse liability (*i.e.*, the likelihood that the drug will be abused) of novel substances. Aarde and colleagues reported that MDPV, similar to methamphetamine, was self-administered in rats and rats consistently self-administered a greater amount of MDPV. As a result, the authors concluded that MDPV poses a substantial threat for compulsive use that is potentially greater than that for methamphetamine.[57]

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[52] P-K Huang et al., *Contrasting Effects of d-Methamphetamine,3,4-Methylenedioxymethamphetamine, 3,4-Methylenedioxypyrovalerone, and 4-Methylmethcathinone on Wheel Activity in Rats*, 126.1 DRUG AND ALCOHOL DEPENDENCE 168, 168-175 (2012).

[53] MH Baumann et al., *Powerful Cocaine-like Actions of 3,4-Methylenedioxypyrovalerone (MDPV), a Principal Constituent of Psychoactive 'Bath Salt' Products*, 38.4 NEUROPSYCHOPHARMACOLOGY 552, 552-562 (2013); WE Fantegrossi et al., *In Vivo Effects of Abused 'Bath Salt' Constituent 3,4-Methylenedioxypyrovalerone (MDPV) in Mice: Drug Discrimination, Thermoregulation, and Locomotor Activity*, 38.4 NEUROPSYCHOPHARMACOLOGY 563, 563-573 (2013); M Gatch et al., *Locomotor Stimulant and Discriminative Stimulus Effects of 'Bath Salt' Cathinones*, 24 BEHAVIORAL PHARMACOLOGY 437, 437-447 (2013); JA Marusich et al., *Pharmacology of Novel Synthetic Stimulants Structurally Related to "Bath Salts" Constituents 3,4-Methylenedioxypyrovalerone (MDPV)*, 87 NEUROPHARMACOLOGY 206, 206-213 (2014).

[54] RI Balster & GE Bigelow, *Guidelines and Methodological Reviews Concerning Drug Abuse Liability Assessment*, 70 DRUG AND ALCOHOL DEPENDENCE s13-40 (2003); LV Panllio & SR Goldberg, *Self-Administration of Drugs in Animals and Humans as a Model and an Investigative Tool* 102.12 ADDICTION 1863, 1863-1870 (2007).

[55] M Gatch et al., *Locomotor Stimulant and Discriminative Stimulus Effects of 'Bath Salt' Cathinones*, 24BEHAVIORAL PHARMACOLOGY 437, 437-447 (2013).

[56] WE Fantegrossi *et al.*, *In Vivo Effects of Abused 'Bath Salt' Constituent 3,4-Methylenedioxypyrovalerone (MDPV) in Mice: Drug Discrimination, Thermoregulation, and Locomotor Activity*, 38.4 NEUROPSYCHOPHARMACOLOGY 563, 563-573 (2013).

[57] SM Aarde et al., *The Novel Recreational Drug 3,4-Methylenedioxypyrovalerone (MDPV) is a Potent Psychomotor Stimulant: Self-administration and Locomotor Activity in Rats*, 71 NEUROPSYCHOPHARMACOLOGY 130, 130-140 (2013); M Gatch et al., *Locomotor Stimulant and Discriminative Stimulus Effects of 'Bath Salt' Cathinones*, 24 BEHAVIORAL PHARMACOLOGY 437, 437-447 (2013); JA Marusich et al., *Pharmacology of Novel Synthetic Stimulants Structurally Related to "Bath Salts" Constituents 3,4-Methylenedioxypyrovalerone (MDPV)*, 87 NEUROPHARMACOLOGY 206, 206-213 (2014).

The Substance's History and Current Pattern of Abuse

DEA forensic laboratories have analyzed drug exhibits received from state, local, or federal law enforcement agencies that were found to contain MDPV. MDPV, like methamphetamine, is commonly encountered in the form of powders, capsules, and tablets. Information from published scientific studies indicate that the most common routes of administration for MDPV is ingestion by swallowing capsules or tablets or nasal insufflation by snorting the powder. The reported average amount of use of MDPV ranged widely (from approximately 25 milligrams – 5 grams) depending on the substance, duration of intake, and route of administration.[58] The dose range for snorting MDPV ranges from as little as 25 milligrams to as much as 5 grams. Even low doses can cause psychoactive effects. Ingestion of high doses of MDPV has been associated with severe adverse effects such as psychosis, paranoia, and death. Similarly, methamphetamine has been reported to cause psychoactive effects at low doses (range from 5 to 30 mg) and psychosis at higher doses.[59] Evidence from poison centers, published case reports, and law enforcement encounters suggest that the main users of MDPV, similar to synthetic cathinones, are young adults. There is evidence that MDPV may be co-ingested with other substances including other synthetic cathinones, pharmaceutical agents, or other recreational substances.

The Scope, Duration and Significance of Abuse

According to forensic laboratory data as reported by the National Forensic Information Laboratory System (NFLIS), MDPV started to be encountered by law enforcement in December 2009. Through January 2017, NFLIS has reported 9,511 law enforcement encounters involving MDPV (query date February 27, 2017, Federal, State, and local laboratories). Additionally, large seizures of MDPV have occurred by CBP.

Risk to Public Health

MDPV has been reported to cause a number of stimulant-like adverse effects. The clinical presentation of intoxication from MDPV is like that seen with methamphetamine and other substances (*e.g.,* cathinone, methcathinone, MDMA, amphetamine, methamphetamine, and cocaine) that have a stimulant effect on the central nervous system. Adverse effects associated with the consumption of MDPV include palpitations, hyperthermia, seizures, hyponatremia, bruxism, sweating, hypertension, tachycardia, headache, thirst, mydriasis, tremor, fever, confusion, psychosis, paranoia, hallucinations, combativeness, agitation, and death. Published case reports describing MDPV related adverse effects are summarized below.

- The death of a 39-year-old male was reported by Wyman *et al.*[60] Family members indicated that the male, who had a history of schizophrenia, depression, and drug abuse,

[58] ADVISORY COUNCIL ON THE MISUSE OF DRUGS, *Consideration of the Cathinones.* (Iversen), London, (Mar. 31, 2010).
[59] CC Cruickshank & KR Dyer, *A Review of the Clinical Pharmacology of Methamphetamine*, 104.7 ADDICTION1085, 1085-1099 (2009).
[60] JF Wyman et al., *Postmortem Tissue Distribution of MDPV Following Lethal Intoxication by "Bath Salts"*, 37 J. ANALYTICAL TOXICOLOGY 182, 182-185 (2013).

had been snorting "bath salts." The subject was found dead in his bed. Empty jars of "bath salts" ("TranQuility" and "Infinity") and synthetic cannabinoids ("Demon" and "Flame") were found in the trash. The cause of death was acute MDPV intoxication.[43]

- A 40-year-old male injected and snorted MDPV and became agitated, aggressive, and suffered from cardiac arrest. He later developed hyperthermia, rhabdomyolysis, coagulopathy, acidosis, anoxic brain injury and died. Other symptoms included mydriasis, labored breathing, and increased heart rate.[61]

- A 39-year-old delusional man with a medical history of depression, back pain, and alcoholism was found outside his residence talking to himself and wandering about in clothes inappropriate for the weather. Law enforcement took the victim to the emergency room. Medical staff noted whitish powder around the mouth of the victim. The victim admitted to using "bath salts." The victim became tachycardic, hyperthermic, followed by bradycardia. After further attempts to save him the victim died. MDPV was identified in samples from the decedent. Autopsy report cited MDPV toxicity to be the primary factor contributing to the death.[62]

- A 46-year-old male was found dead after several days of using the bath salt "Drone." The decedent had complained of weakness, difficulty walking, increased falling, nausea and vomiting prior to his death. He had a history of drug use and diabetes. Toxicology results confirmed MDPV in blood and urine. The cause of death was determined to be diabetic ketoacidosis in a setting of MDPV abuse.[63]

- A 40-year-old male was found dead at his home. The decedent was alleged to have been snorting and smoking bath salts. The decedent had HIV and had taken a variety of medications. Toxicology results confirmed MDPV in blood and urine. Death was determined to be attributed to relevant natural causes in a setting of MDPV abuse.[46]

- Rohrig described the case of a 21-year-old who was struck and killed by a van after he ran into oncoming traffic.[64] A witness reported that the decedent was let out of the car on the side of a local interstate after he acted wildly and belligerently after ingesting "bath salts" and smoking "K2" (a synthetic cannabinoid containing product). MDPV was detected in serum samples from the decedent.

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[61] BL Murray et al., *Death Following Recreational Use of Designer Drug "Bath Salts" Containing 3,4-Methylenedioxypyrovalerone (MDPV)*, 8 J. MED. TOXICOLOGY 69, 69-75(2012).
[62] K Kesha et al., *Methylenedioxypyrovalerone ("Bath Salts") Related Death: Case Report and Review of the Literature*, 58.6 J. FORENSIC TOXICOLOGY 1654, 1654-1659 (2013).
[63] TH Wright et al., *Deaths Involving Methylenedioxypyrovalerone (MDPV) in Upper East Tennessee*, 58.6 J. FORENSIC TOXICOLOGY, 1558, 1558-1562 (2013).
[64] T Rohrig, California Association of Toxicologist(CAT) Proceedings, *Designer Drugs- The Future of Drug Abuse? Pharmacology of Cathinone Analogs AKA "Bath Salts"*. May 5-6, Napa, CA (2011).

- A 30-year-old man who reportedly spent the day snorting bath salts jumped from a second story window of a hotel. He was found dead in a creek near the hotel. MDPV was detected in blood samples from this individual.[65]

- A 25-year-old man was transported to the emergency department after he was found with marked agitation and altered mental status. He presented with elevated blood pressure, pulse rate and temperature. He also suffered from mydriasis, combativeness, and other symptoms. He was treated at the hospital by extubation, and hemodialysis. Urine tested positive for MDPV. He recovered and was released from the hospital on day 18.[66]

- Sadeg *et al.* described a case of a 47-year-old man who was brought to the emergency department by firemen for behavioral changes with delirious thoughts.[67] His wife described the man as restless and soliloquizing for the last three days. At the hospital the patient was suspicious, anxious, and agitated. He suffered an acute episode of delirium with persecution, megalomaniac themes and focused on the feeling of being watched and monitored as well as having the power to remotely control electrical circuits. He was treated with antipsychotics and benzodiazepines. Testing of products purchased by the patient on the Internet and ingested identified MDPV. The patient reported experiencing euphoria, increase energy with restlessness, empathy, and openness. Analysis of serum of patient also identified MDPV. The patient recovered the following day and treatment ceased. However, three weeks after the patient was discharged he took again to craving the MDPV-containing product which led to a new occurrence of psychosis with visual hallucinations.

- Penders and Gestring reported three cases of paranoid psychotic delirium (presenting as paranoid hallucinatory psychosis) following the alleged abuse of "bath salts" containing MDPV.[68] Interestingly, in these three cases of delirium, some memory loss was reported during the time of abuse of the "bath salts."

- Kriikku *et al.* described cases involving drivers suspected of being under the influence of drugs (DUID) in Finland.[69] Blood samples from individuals suspected of DUIDs from August 2009 to August 2010 were screened for the presence of MDPV. Of 3000 samples tested, 259 were found to be positive for MDPV. The concentration of MDPV ranged from 0.020 – 8.4 mg/L (limit of detection is 0.003 mg/L). Although other drugs may have been detected, the authors concluded that MDPV is a significant problem in DUID cases in Finland.

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[65] JW Spencer et al., *Acute Psychiatric, Cardiopulmonary, and Neurologic Effects of Laboratory-Confirmed Use of Methylenedioxypyrovalerone (MDPV) "Bath Salts"*, 49 CLINICAL TOXICOLOGY (Phila)515, 515–562 (2011).
[66] HA Borek & CP Holstege, *Hyperthermia and Multiorgan Failure After Abuse of "Bath Salts" Containing 3,4-Methylenedioxypyrovalerone*, 60.1 ANNUALS OF EMERGENCY MEDICINE103, 103-105 (2012).
[67] N Sadeg et al., *Case Report of Cathinone-Like Designer Drug Intoxication Psychosis and Addiction with Serum Identification*, 13.1 ADDICTIVE DISORDERS & THEIR TREATMENT 38, 38-43 (2014).
[68] TM Penders & R Gestring, *Excited Delirium Following Use of MDPV: 'Bath Salts'*. 36.2 GEN. HOSPITAL PSYCHIATRY 647, 647-650 (2011).
[69] P Kriikku et al., *New Designer Drug of Abuse: 3,4-Methylenedioxypyrovalerone (MDPV). Findings from Apprehended Drivers in Finland*. 210.1-210.3 FORENSIC SCI. INT'L 195, 195-200 (2011).

- A 47-year-old male with a history of psychoactive substance abuse experienced severe adverse effects after ingesting "bath salts" that contained MDPV.[70] Routine drugs of abuse were not detected in biological specimens from the patient. Adverse effects included terrifying hallucinations, coma, seizure, multi-organ failure and ischemic colitis. His symptoms resolved after treatment.

In summary the scientific, medical, case reports, and law enforcement information details serious adverse health effects directly attributable to the abuse of methylone, mephedrone, or MDPV. These substances have been directly compared to substances listed under the sentencing guidelines as to effect and potency.

Synthetic Cannabinoids

Although the abuse of JWH-018, AM-2201 and other synthetic cannabinoids are a more recent challenge for law enforcement and public health, the design and investigation of many of these substances date back more than 20 years. Synthetic cannabinoids are cannabinoid agonists that target the cannabinoid receptor 1. These substances are functionally similar to THC, the main psychoactive ingredient in marijuana. In 2008, synthetic cannabinoids were detected in herbal smoking blends and many generations have been encountered since the initial finding in an attempt to stay ahead of regulatory controls. According to some reports the intoxication or high produced by synthetic cannabinoids is more intense than that produced by cannabis. The increased affinity of these substances for the cannabinoid receptor relative to THC and the greater activation of the receptor are attributable to the greater potency of these substances relative to marijuana.[71] Thus, an identical amount of JWH-018 or AM-2201 to THC would be expected to show greater intoxication.[72]

JWH-018 and AM-2201 are synthetic cannabinoids and share pharmacological similarities with THC. Serious adverse health effects, as discussed below, are associated with the ingestion of these synthetic cannabinoids. The term "Spice" is commonly used to describe the diverse types of herbal blends that encompass synthetic cannabinoids being laced on plant material for recreational use. Since the emergence of these smokeable herbal product blends, there has been a relatively high incidence of adverse health effects.

These substances are used for their psychoactive properties, and are promoted as "legal" alternatives to marijuana. Synthetic cannabinoids in bulk powder form are smuggled from overseas via common carrier into the United States, and final products for distribution are made in the United States. The powdered forms of JWH-018 or AM-2201 are typically dissolved in solvents (*e.g.*, acetone) before being applied to a plant material or dissolved in a propellant

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[70] G Gavriilidis et al., *"Bath Salts" Intoxication with Multiorgan Failure and Left-sided Ischemic Colitis: A Case Report.* 19.4 HIPPOKRATIA 363, 363-365. (2015).

[71] BK Atwood et al., *JWH018, a Common Constituent of 'Spice' Herbal Blends, is a Potent and Efficacious Cannabinoid CB1 Receptor Agonist*, 160 BRITISH PHARMACOLOGICAL SOC'Y 585, 585-593 (2010); G Griffin et al., *Evaluation of Cannabinoid Receptor Agonists and Antagonists Using the Guanosine-5'-O-(3-[^{35}S]thio)-triphosphate Binding Assay in Rat Cerebellar Membranes*, 285.2 J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 553, 553-560 (1998).

[72] JL Wiley et al., *Hijacking of Basic Research: The Case of Synthetic Cannabinoids*. RTI Press publication No. OP-0007-1111. Research Triangle Park, NC: RTI Press. Retrieved from http://www.rti.org/rtipress.

intended for use in e-cigarette devices. Law enforcement personnel have encountered various application methods including buckets or cement mixers in which plant material and one or more synthetic cannabinoids, such as JWH-018 and/or AM2201, are mixed together, as well as large areas where the plant material is spread out so that a dissolved synthetic cannabinoid can be applied directly.

Adverse health effects following ingestion of JWH-018 have been reported to include short-term memory defects, hypertension, delusions, chest pain, intractable abdominal pain, nausea, vomiting, tachycardia, anxiety, paranoia, auditory and visual hallucinations, seizure, coma and death.[73] Adverse effects following ingestion of AM-2201 have been reported to include convulsions, intractable abdominal pain, nausea, vomiting, confusion, disorientation, psychiatric complications including self-induced lethal trauma and death.[74]

On March 1, 2011, a final order to temporarily place JWH-018 into Schedule I of the CSA was published in the Federal Register (76 FR 11075) upon finding that this substance poses an imminent threat to public safety. On July 9, 2012, JWH-018, AM2201, and 13 other synthetic cannabinoids were permanently placed into Schedule I of the CSA following congressional action (section 1152 of Food and Drug Administration Safety and Innovation Act (FDASIA)). The FDASIA also amended the CSA by adding the term "cannabimimetic agents" which was defined to include substances within defined structural classes that are demonstrated by binding studies and functional assays to be cannabinoid receptor type 1 (CB1 receptor) agonists.

The data available and reviewed for JWH–018 and AM-2201 indicate that these synthetic cannabinoids have a high potential for abuse, no currently accepted medical use in treatment in the United States and lack an accepted safety for use under medical supervision.

JWH-018

JWH-018 is a synthetic cannabinoid of the indole-derived cannabinoids and was one of the initial synthetic cannabinoids identified in the smokable herbal products. The synthesis and evaluation of JWH-018 had been published in the scientific literature many years prior to discovery of the substance on plant material. Early clinical reports documenting JWH-018 abuse note patients presenting with symptoms atypical of marijuana use, noting extreme agitation, syncope, tachycardia, and visual and auditory hallucinations.[75]

[73] SMR Gurney et al., *Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs*, 26.1 FORENSIC SCI. REV., 54, 54-78 (2014).
[74] S Gurney et al., *Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs*, 26.1 FORENSIC SCI. REV. 53, 54-78 (2014); A. Patton et al., *K2 Toxicity: Fatal Case of Psychiatric Complications Following AM2201 Exposure*, 58.6 J. FORENSIC SCI. 1676, 1676-1680 (2013).
[75] D Vearrier & KC Osterhoudt, *A Teenager With Agitation: Higher Than She Should Have Climbed*, 26 PEDIATRIC EMERGENCY CARE 462, 462–465 (2010); H Muller et al., *The Synthetic Cannabinoid Spice as a Trigger for an Acute Exacerbation of Cannabis Induced Recurrent Psychotic Episodes*, 118 SCHIZOPHRENIA RES. 309, 309–310 (2010); S Every-Palmer, *Warning: Legal Synthetic Cannabinoid-Receptor Agonists Such As JWH-018 May Precipitate Psychosis in Vulnerable Individuals*, 105 ADDICTION 1859, 1859–1860 (2010); AB Schneir et al., *"Spice" Girls: Synthetic Cannabinoid Intoxication*, 40.3 J. EMERGENCY MED. 296, 296-299 (2010).

Scientific Evidence of the Substance's Pharmacological Effect

The effect of the acute administration of JWH-018 (0.01-6 mg/kg i.p.) on sensorimotor function in male CD-1 mice was compared to those effects caused by the administration of THC (0.01-6 mg/kg i.p.).[76] JWH-018 inhibited sensorimotor responses at the lower doses (0.01-0.1 mg/kg), reduced spontaneous locomotion at intermediate to high doses (1-6 mg/kg) and induced convulsions, myoclonia and hyperreflexia at high dose (6 mg/kg). THC reduced sensorimotor responses in mice but it did not inhibit spontaneous locomotion and it did not induce neurological alterations. JWH-018 was more potent than THC in this study and the greater activity could be due to the higher affinity at the CB1 receptor.

Cannabinoid agonists elicit a characteristic cluster of effects in laboratory animals. This cluster of classical endpoints of analgesia, hypothermia, catalepsy, and locomotor suppression is known as the cannabinoid tetrad and is a classic test. JWH-018 elicits characteristic tetrad effects in mice after intraperitoneal injection.[77] Wiley and colleagues found JWH-018 to be 2.5 times more potent than THC in the tetrad battery.[78] In another tetrad study, JWH-018 was found to be more potent than THC by inhalation and intraperitoneal injection.[79] These results demonstrate that JWH-018 elicits a THC-like profile in a test battery in mice and would be likely to produce cannabimimetic discriminative stimulus effects in rodents, confirmed below, and would be predicted to have marijuana-like effects in humans. JWH-018 displayed greater potency than THC in the three studies detailed above. Drug discriminative studies selective for cannabinoid agonism is a powerful tool comparing effects of cannabinoids and is highly selective for CB1 receptor. The results are highly predictive of subjective effects for cannabis.[80] This is important for it would be inappropriate to dose humans with substances such as JWH-018 in the absence of safety evaluations. Data from published drug discrimination studies indicate that JWH-018 is similar to THC in its discriminative stimulus effects and it substitutes fully for the discriminative stimulus effects of THC in animals trained to discriminate THC from its vehicle.[81] This study reported potencies (ED_{50}) of 0.18 mg/kg and 0.56 mg/kg for JWH-018 and THC, respectively. Thus JWH-018 is approximately three times more potent than THC in this assay. Jarbe *et al.* found JWH-018 to be approximately 8 times more potent than THC in rats.[82] In monkeys, the ED_{50} values were reported as 0.013 mg/kg for JWH-018 and 0.044 for THC.[83]

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[76] A Ossato et al., *JWH-018 Impairs Sensorimotor Functions in Mice*, 300 NEUROSCIENCE 174, 174-188 (2015).
[77] LK Brents et al., *Monohydroxylated Metabolites of the K2 Synthetic Cannabinoid JWH-073 Retain Intermediate to High Cannabinoid 1 Receptor (CB1R) Affinity and Exhibit Neutral Antagonist to Partial Agonist Activity*, 83.7 BIOCHEMISTRY AND PHARMACOLOGY 952, 952–961 (2012).
[78] JL Wiley et al., *1-Pentyl-3-Phenylacetylindoles and JWH-018 Share In Vivo Cannabinoid Profiles in Mice*, 123.1-123.3 DRUG AND ALCOHOL DEPENDENCE 148, 148–153 (2012).
[79] R Marshell et al., *In Vivo Effects of Synthetic Cannabinoids JWH-018 and JWH-073 and Phytocannabinoid Δ^9-THC in Mice: Inhalation Versus Intraperitoneal Injection*, 124 PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR 40, 40-47 (2014).
[80] RL Balaster & WR Prescott, *Δ^9-Tetrahydrocannabinol Discrimination in Rats as a Model for Cannabis Intoxication*, 16 NEUROSCIENCE AND BIOBEHAVIORAL REV. 55, 55-62 (1992).
[81] MB Gatch & MJ Forester, *Δ^9-Tetrahydrocannabinol-Like Discriminative Stimulus Effects of Compounds Commonly Found in K2/Spice, 8* BEHAVIORAL PHARMACOLOGY 750, 750-757 (2014).
[82] Jarbe et al., *Cannabinergic Aminoalkylindoles, Including AM678=JWH018 Found in 'Spice', Examined Using Drug (Δ9-THC) Discrimination for Rats*, 22.5-22.6 BEHAVIORAL PHARMACOLOGY 498, 498–507 (2011).
[83] BC Ginsburg et al., *JWH-018 and JWH-073: Δ^9-Tetrahydrocannabinol-Like Discriminative Stimulus Effects in Monkeys*, 340.1 J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 37, 37-45 (2012).

Adverse Effects/Deaths Involving JWH-018

Adverse health effects following ingestion of JWH-018 (as confirmed by toxicology results) have included: short-term memory defects, hypertension, delusions, chest pain, intractable abdominal pain, nausea, vomiting, tachycardia, anxiety, paranoia, auditory and visual hallucinations, seizure, coma and death.[84]

JWH-018 was confirmed in 8 of 29 synthetic cannabinoid presentations in response to recreational use.[85] The acute adverse reactions displayed included restlessness/agitation, changes in perception/hallucinations, vertigo, somnolence, anesthesia/paraesthesis, shivering/shaking, tachycardia, other electrocardiographic changes, hypertension, thoratic pain, nausea/vomiting, mydriasis, and conjunctival hyperaemia. Seizures developed in 1 of the 8 JWH-018 patients.

- According to the data gathered by DEA, in September 2011, a 19-year-old male complained of cramping and vision changes, and was transported to a local emergency facility for further assessment. The victim was admitted but ultimately died four days later. Upon autopsy, postmortem analysis demonstrated extensive multi-organ failure. Postmortem toxicology detected JWH-018N, a metabolite of JWH-018. The cause of death was determined to be excited delirium which was associated with drug toxicity. The manner of death was ruled accidental.

- In a case report published by Wikstrom *et al.*, a 26-year-old male ingested multiple synthetic substances, ultimately resulting in his death.[86] Postmortem toxicology results obtained during autopsy revealed a high concentration of methoxetamine (MXE), along with three different synthetic cannabinoids (AM694, AM2201 and JWH-018). Authors stated that the high MXE concentration pointed to an acute fatal intoxication with MXE; however, the presence of the three synthetic cannabinoids may have contributed to the death.

NFLIS reports for JWH-018

According to forensic laboratory data as reported by the National Forensic Information Laboratory System[87,88] (NFLIS), JWH-018 was first encountered by law enforcement in August

[84] SMR Gurney et al., *Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs*, 26.1 FORENSIC SCI. REV. 54, 54-78 (2014).
[85] M Hermanns-Clausen et al., *Acute Toxicity Due to the Confirmed Consumption of Synthetic Cannabinoids: Clinical and Laboratory Findings*, 108.3 ADDICTION 1-11 (2012).
[86] M Wikstrom et al., *An Accidental Fatal Intoxication with Methoxetamine*, 37.1 J. ANALYTICAL TOXICOLOGY PSYCHOPHARMACOLOGY 43, 43-46 (2013).
[87] The NFLIS is a program of the DEA, Diversion Control Division. NFLIS systematically collects drug identification results and associated information from drug cases submitted to and analyzed by Federal, State and local forensic laboratories. NFLIS represents an important resource in monitoring illicit drug abuse and trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS is a comprehensive information system that includes data from forensic laboratories that handle approximately 98% of an estimated nearly 1.0 million distinct annual State and local drug analysis cases. NFLIS includes drug chemistry results from completed analyses only.
[88] While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 Fed. Reg. 77330, 77332, (Dec. 12, 2011).

2009. Through January 2017, NFLIS has reported 7,144 law enforcement encounters involving JWH-018 (query date February 27, 2017, Federal, State, and local laboratories).

Summary JWH-018

JWH-018 is comparable pharmacologically to the Schedule I substance THC. JWH-018 binds to actives the CB1 receptor, the same receptor as THC. In standard behavioral studies, JWH-018 is at least three times more potent than THC. It was not found to be less potent than THC in any study. Ginsburg and colleagues stated that JWH-018 has abuse liability similar to THC and possibly greater and that anecdotal reports of intoxication suggest alternative sites of action.[89] Further, the short duration and increased efficacy of JWH-018 could lead to more frequent and habitual use.[47]

AM-2201

AM-2201 is a synthetic cannabinoid of the indole-derived cannabinoids and was encountered around the time JWH-018 was temporarily controlled by the DEA. AM-2201 is similar in structure to JWH-018, differing by the addition of a single fluorine atom. Information regarding AM-2201 was initially published in the patent literature many years prior to the encounter of the substance by law enforcement. Early clinical reports documenting the abuse of AM-2201 note patients present to emergency departments with a host of symptoms many of which are atypical of marijuana use, noting extreme agitation, syncope, tachycardia, and visual and auditory hallucinations.[90]

Scientific Evidence of the Substance's Pharmacological Effect

Data from a published drug discrimination studies indicate that AM-2201 is similar to THC in its discriminative stimulus effects and it substitutes fully for the discriminative stimulus effects of THC in animals trained to discriminate THC from its vehicle.[91] This study reported potencies (ED_{50}) of 0.11 mg/kg and 0.56 mg/kg for AM-2201 and THC, respectively. Thus AM2201 is approximately five times more potent than THC in this assay.

Adverse Effects/Deaths Involving AM-2201

[89] BC Ginsburg et al., *JWH-018 and JWH-073: Δ^9-Tetrahydrocannabinol-Like Discriminative Stimulus Effects in Monkeys*, 340.1 J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 37, 37-45 (2012).
[90] D Vearrier & KC Osterhoudt, , 26 PEDIATRIC EMERGENCY CARE462, 462–465 (2010); H Muller *et al*., *The Synthetic Cannabinoid Spice as a Trigger for an Acute Exacerbation of Cannabis Induced Recurrent Psychotic Episodes*, 118 SCHIZOPHRENIA RES.309, 309–310 (2010); S Every-Palmer, *Warning: Legal Synthetic Cannabinoid-Receptor Agonists Such As JWH-018 May Precipitate Psychosis in Vulnerable Individuals*, 105 ADDICTION 1859, 1859–1860 (2010); AB Schneir et al., *"Spice" Girls: Synthetic Cannabinoid Intoxication*, 40.3 J. EMERGENCY MED. 296, 296-299 (2010).
[91] MB Gatch & MJ Forester, *Δ^9-Tetrahydrocannabinol-Like Discriminative Stimulus Effects of Compounds Commonly Found in K2/Spice*, 8 BEHAVIORAL PHARMACOLOGY 750, 750-757 (2014).

Adverse effects following ingestion of AM-2201 (as confirmed by toxicology results) have included: convulsions, intractable abdominal pain, nausea, vomiting, confusion, disorientation, psychiatric complications including self-induced lethal trauma and death.[92]

- In August 2011, a 23-year-old male suffered self-inflicted lethal trauma in the form of sharp-force neck wounds following ingesting a synthetic cannabinoid. A high concentration of AM-2201 was found in both postmortem blood and evidence collected.[93]

- According to the data gathered by DEA, in February 2012, a 26-year-old male was found dead in his residence. He had a history of abusing natural and synthetic cannabinoids. The autopsy was essentially negative, however the comprehensive postmortem toxicology analysis revealed presence of three synthetic cannabinoids in the blood (AM-2201, JWH-122 and JWH-210), results further confirmed by an outside laboratory. The cause of death is ascribed to "sudden cardiac death associated with the use of synthetic cannabinoids. The manner of death is classified as accidental.

- According to the data gathered by DEA, in March 2012, a 16-year-old male was found dead in a hot tub at his parent's residence. The medical examiner concluded that the young man was intoxicated by the synthetic cannabinoid AM-2201 at the time of his death. Results of toxicology testing for both the decedent's blood and evidence collected were positive for AM-2201. Detailed blood toxicological tests revealed no additional therapeutic or illicit drugs that could have caused or contributed to his death. A full autopsy showed no evidence of natural diseases or significant traumatic injuries. The manner of death was classified as accidental.

- In a case report published by Wikstrom *et al.*, a 26-year-old male ingested multiple synthetic substances, ultimately resulting in his death.[94] Postmortem toxicology results obtained during autopsy revealed a high concentration of methoxetamine (MXE), along with three synthetic cannabinoids (AM-694, AM-2201 and JWH-018). Authors stated that the high MXE concentration pointed to an acute fatal intoxication with MXE; however, the presence of the three synthetic cannabinoids may have contributed to the death.

- A 19-year-old male in his normal state of health had a witnessed generalized 1- to 2-min convulsion while smoking a product "Happy Tiger Incense."[95] He vomited and had second generalized convulsions during transport. On admission to the emergency department, he had blood pressure 177/82 mm Hg, heart rate 84 beats/min. JWH-018, JWH-081, JWH-250, and AM-2201 were identified in the product.

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[92] SMR Gurney et al., *Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs*, 26.1 FORENSIC SCI. REV. 53, 53-78 (2014); AL Patton et al., *K2 Toxicity: Fatal Case of Psychiatric Complications Following AM2201 Exposure*, 58.6 J. FORENSIC SCIENCES 1676, 1676-1680 (2013).

[93] AL Patton et al., *K2 Toxicity: Fatal Case of Psychiatric Complications Following AM2201 Exposure*, 58.6 J. FORENSIC SCI., 1776, 1676-1680 (2013).

[94] M Wikstrom et al., *An Accidental Fatal Intoxication with Methoxetamine*, 37.1 J. ANALYTICAL TOXICOLOGY PSYCHOPHARMACOLOGY 43, 43-46 (2013).

[95] AB Schnier & T Baumbacher, *Convulsions Associated with the Use of a Synthetic Cannabinoid Product*, 8 J. MED.L TOXICOLOGY 62, 62-64 (2012).

- A 20-year-old male smoked the product "Black Mamba" and rapidly after smoking, he had a generalised self-terminating tonic-clonic convulsion.[96] After 2 hours of observation in the Emergency Department (ED), the patient self-discharged against medical advice. Analysis of urine detected metabolites of AM-2201; no other drugs were detected on extensive analytic screening.

NFLIS reports for AM-2201

According to forensic laboratory data as reported by the National Forensic Information Laboratory System (NFLIS), AM-2201 was first encountered by law enforcement in February 2010. Through May 2015, NFLIS has reported 24,165 law enforcement encounters involving AM-2201 (query date February 27, 2017, Federal, State, and local laboratories). In 2013, AM-2201 was the most commonly reported synthetic cannabinoid in drug seizures and was the eighth most encountered substance by law enforcement. It ranked above common substances of abuse such as amphetamine at #11 and PCP at #19 of all drugs reported by state and local forensic labs.

Summary AM-2201

AM-2201 is comparable pharmacologically to the Schedule I substance THC. AM-2201 binds to actives the CB1 receptor, the same receptor as THC. In standard behavioral studies, AM-2201 is at least 5-times more potent than THC. It was not found to be less potent than THC in any study.

In summary, pharmacological studies and clinical reports detail the drug effects of JWH-018 and AM-2201. Animal studies are directly compared to THC and demonstrate an increased potency of JWH-018 and AM-2201 relative to THC. Additionally, serious adverse effects including coma, seizures and death following use of products containing JWH-018 and/or AM-2201 have been documented and law enforcement has detailed information regarding the trafficking and manufacture of the substances and their respective products.

Methylenedioxymethamphetamine

Methylenedioxymethamphetamine (MDMA) is a Schedule I controlled substance, meaning it has a high potential for abuse and no approved medical use. It is well established that MDMA has powerful pharmacological effects and is being abused. The substance has the capacity to cause lasting physical harm and continues to be a threat to public health and safety.[97] As a result of the intense euphoria common to MDMA, there is depletion of neurotransmitters resulting in depression and common to other drugs of abuse, MDMA triggers substance induced anxiety, panic, psychosis, and depression.

The Sentencing Commission's sentencing guidelines for MDMA, originally based on research that demonstrated neurotoxicity in users, has been strengthened since 2001 by ongoing

[96] D McQuade et al., *First European Case of Convulsions Related to Analytically Confirmed Use of the Synthetic Cannabinoid Receptor Agonist AM-2201*, 69.3 EUROPEAN J. CLINICAL PHARMACOLOGY 373, 373-376 (2013).
[97] AC Parrott, *MDMA is Certainly Damaging after 25 Years of Empirical Research: a Reply and Refutation of Doblin et al*, 29.2 HUMAN PSYCHOPHARMACOLOGY 109, 109-119 (2014).

research and publications utilizing updated and more precise measurements which repeatedly conclude that MDMA, even while taken in low doses, is neurotoxic. The neurochemistry and adverse health effects of MDMA have not changed. The substance continues to be both reinforcing and a catalyst for neurological disorders. There is a misbelief among users that the drug is safe even amidst the reports of severe acute toxicity and deaths. Particularly concerning is the rise in MDMA use by teenagers. The number of 10th and 12th grade students that have used MDMA over the past year is approaching the highest levels seen in the past decade, while over the same time period, there has been a dramatic drop in students in grades 8, 10 and 12 who feel there is a "great risk" in using MDMA once or twice, demonstrating that the perception that MDMA is a safe drug is intensifying.[98]

As described by the National Institute on Drug Abuse (NIDA), MDMA is a synthetic, psychoactive drug that is chemically similar to the stimulant methamphetamine and the hallucinogen mescaline. MDMA is a powerful recreational drug of abuse resulting in toxic outcomes to serotonin neurons within the cortex and the hippocampus, amongst other areas.[99] The desired effects of MDMA have included increased energy, euphoria and positive social and emotional feelings, accompanying these effects are a host of harms to include potential hypertension (increased blood pressure), hyperthermia (increased body temperature) and hyponatremia (electrolyte disturbance resulting in low levels of sodium) exacerbated by antidiuresis (reduced urine volume). There have been a number of peer-reviewed published studies clearly demonstrating the neurotoxicity of MDMA, especially in the form of a decrease in serotonin transporter (SERT) density and binding following MDMA use.[100] In addition to imaging studies confirming that MDMA exposure can lead to neurotoxicity, multiple recent studies have demonstrated the negative effects of MDMA use on memory. Results of clinical testing of MDMA users have demonstrated the following: (1) abnormal function of the hippocampus during memory function tests;[101] (2) significantly worse performance of male MDMA users on the tasks that correlate to cognitive flexibility and on the combined executive function task;[102] (3) using fMRI, MDMA was shown to be associated with reduced associative memory performance;[103] (4) a recently published meta-analysis of multiple studies regarding MDMA users reduced the outcomes to a single common denominator to see the average effect and concluded that there was a significant decrement in the MDMA user as compared to control subjects regarding verbal memory;[104] and (5) cortex deficiencies during a word recognition task

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[98] National Press Release, LD Johnston et al., *Marijuana Use Continues to Rise Among U.S. Teens, While Alcohol Use Hits Historic Lows*, University of Michigan News Service, Ann Arbor, MI (December 14, 2011), *available at* http://www.monitoringthefuture.org/press.html (last visited Mar. 2, 2017).

[99] SJ Kish et al., *Decreased Cerebral Cortical Serotonin Transporter Binding in Ecstasy Users: a Positron Emission Tomography/[(11)C]DASB and Structural Brain Imaging Study*, 133 BRAIN, 1779, 1779-1797 (2010).

[100] UD McCann et al., *Positron Emission Tomographic Evidence of Toxic Effect of MDMA ("Ecstasy") on Brain Serotonin Neurons in Human Beings*, 352.9138 LANCET 1433, 1433-1437 (1998); RL Cowan, *Neuroimaging Research in Human MDMA Users: a Review,189.4* PSYCHOPHARMACOLOGY (BERL) 539, 539-556 (2007).

[101] LK Jacobsen et al., *Preliminary Evidence of Hippocampal Dysfunction in Adolescent MDMA ("Ecstasy") Users: Possible Relationship to Neurotoxic Effects*, PSYCHOPHARMACOLOGY (BERL)173, 3-4, 383-90 (2004).

[102] NA von Geusau et al., 175.3 *Impaired Executive Function in Male MDMA ("ecstasy") Users*, PSYCHOPHARMACOLOGY (BERL) 331, 331-41 (2004).

[103] G Jager et al., *Assessment of Cognitive Brain Function in Ecstasy Users and Contributions of Other Drugs of Abuse: Results From an FMRI Study*, 33.2 NEUROPSYCHOPHARMACOLOGY 247, 247-258 (2008).

[104] G Rogers et al., *The Harmful Health Effects of Recreational Ecstasy: a Systematic Review of Observational Evidence*, 13.6 HEALTH TECH. ASSESSMENT xii, iii-iv, ix-xii, 1-315(2009).

in MDMA users.[105] Lastly, in an even more compelling argument that MDMA exposure can lead to long-lasting neurotoxicity, Morgan *et al.* looked at verbal memory between current and former MDMA users, as well as polydrug users and control volunteers with no prior drug use history, and demonstrated a deficiency in verbal memory in those users who were abstinent from MDMA use on average for two years prior to testing.[106]

Clinical case reports document that regular MDMA use can be associated with chronic psychiatric symptoms after cessation of drug use. In addition to neurocognitive and neurobehavioral deficits linked to MDMA's toxicity, serious cardiovascular and respiratory complications and liver damage have been reported in connection with MDMA use. A case series published in the Journal of Intensive Care Medicine described twelve patients that presented to the emergency department with MDMA toxicity resulting in 4 patients with permanent neurological, musculoskeletal and/or renal deficits and 2 deaths, all directly resultant from MDMA ingestion.[107] Other overdose events have been reported and some with tragic outcomes.[108]

Similar to other drugs of abuse, studies demonstrate MDMA dependence is associated with intensity and lifetime use.[109] MDMA-associated overdoses commonly occur with polysubstance use, possibly used to enhance the effects of the drug. In the absence of national data for MDMA overdose deaths, the Florida Department of Law Enforcement maintains a database for drug-related deaths in Florida. From 2003 to 2010, there were a total of 388 MDMA-related deaths and MDMA was implicated as the cause of death in 86 of these deaths. This remains especially concerning as MDMA pills have increased in the amount of MDMA they contain in recent years.[110]

MDMA remains a dangerous drug of concern and the short- and long-term adverse health effects are well documented. DEA continues to encounter MDMA in our investigations. Also, morbidity and mortality information continues to be collected connected to MDMA abuse. MDMA is not a benign drug, as some suggest.

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[105] AP Burgess et al., *Event Related Potential (ERP) Evidence for Selective Impairment of Verbal Recollection in Abstinent Recreational Methylenedioxymethamphetamine ("Ecstasy")/Polydrug Users*, 216.4 PSYCHOPHARMACOLOGY (BERL) 545, 545-556 (2011).

[106] MJ Morgan et al., *Ecstasy (MDMA): Are the Psychological Problems Associated With Its Use Reversed By Prolonged Abstinence?*, 159.3 PSYCHOPHARMACOLOGY (BERL) 294, 294-303 (2002).

[107] P Armenian et al., *Multiple MDMA (Ecstasy) Overdoses at a Rave Event: A Case Series*, 28.4 J, INTENSIVE CARE MED. 252, 252-258 (2012).

[108] Morbidity and Mortality Weekly Report, *Ecstasy Overdoses at a New Year's Eve Rave – Los Angeles, CA, 2010*. CENTER FOR DISEASE CONTROL 59, 22, 677-681 (June 11, 2010); Morbidity and Mortality Weekly Report, *Illness and Deaths Among Persons Attending an Electronic Dance Music Festival – New York City, 2013*. CENTER FOR DISEASE CONTROL 63, 50, 1195-1198 (December 19, 2014); CM Milroy, *"Ecstasy" Associated Deaths: What is the Fatal Concentration? Analysis of a Case Series*, 7.3 FORENSIC SCI. MED. AND PATHOLOGY 248, 248-252 (2011); F Schifano, *A Bitter Pill. Overview of Ecstasy (MDMA, MDA) Related Fatalities*, 173 PSYCHOPHARMACOLOGY (BERL)242, 242-248 (2004).

[109] N Bruno & PP Battaglini, *Integrating Perception and Action Through Cognitive Neuropsychology (Broadly Conceived)*, 25 COGNITIVE NEUROPSYCHOLOGY 5, 5-7, (2008); JW Hopper et al., *Incidence and Patterns of Polydrug Use and Craving for Ecstasy in Regular Ecstasy Users: an Ecological Momentary Assessment Study*, 83.3 DRUG AND ALCOHOL DEPENDENCE 221, 221-235 (2006).

[110] *Recent Changes in Europe's MDMA/Ecstasy Market*, EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION, (EMCCDA Rapid communication, Publication Office of the E.U., Luxembourg), April 2016.

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Thank you for the opportunity to share the views of the Department of Justice. We look forward to working with the Commission on this important issue.