U. S. Department of Justice
Drug Enforcement Administration
Diversion Control Division

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August 3, 2017

The Honorable William H. Pryor, Jr.
Acting Chair
United States Sentencing Commission
One Columbus Circle, NE
Suite 2-500, South Lobby
Washington, D.C. 20002-8002

Dear Judge Pryor:

In June of 2017, the Commission published an issue for public comment on MDMA and methylone, as well as other synthetic cathinones.[1] Please see below for the Drug Enforcement Administration's responses on these issues. Thank you in advance for considering our thoughts.

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Issue 1

"The Commission invites general comment on whether, and if so how, the guidelines for MDMA/Ecstasy trafficking should be changed. As stated above, the marihuana equivalency of MDMA is 1 gm of MDMA = 500 gm of marihuana. Is the marihuana equivalency for MDMA appropriate? Should the Commission establish a different equivalency for MDMA? If so, what equivalency should the Commission provide and on what basis?
The Commission further seeks comment on any relevant developments in the scientific literature on the health effects of MDMA use since the Commission published its MDMA Report and last amended the marihuana equivalency for MDMA in 2001. The Commission also seeks comment about whether there have been changes in MDMA distribution and usage patterns, such as marketing to or prevalence of use among youth, since 2001. For example, how is MDMA typically manufactured, distributed, and marketed today? How does MDMA compare to other controlled substances referenced in §2D1.1 in terms of health effects (including addictiveness and abuse potential), marketing and trafficking patterns, and potency by dosage unit? How should the Commission assess the harms of MDMA relative to those of other controlled substances?
Finally, the Commission seeks comment on whether since 2001 there have been any developments to suggest that the Commission, in addition to or instead of establishing a different equivalency for MDMA, should revise the "typical weight per unit" measure set forth in Application Note 9 to §2D1.1, which is currently set at 250 mg for MDMA. If so, what are those developments? How should the Commission revise the "typical weight per unit" measure set forth for MDMA?"

Drug seizure data demonstrate that MDMA (3,4-methylenedioxymethamphetamine, often

1 UNITED STATES SENTENCING COMMISSION, SENTENCING GUIDELINES FOR UNITED STATES COURTS: REQUEST FOR PUBLIC COMMENT BAC 2210-40 (2017) https://www.ussc.gov/sites/default/files/pdf/amendment-process/federal-register-notices/20170622_fr_comment.pdf.

sold as "Ecstasy"), is still a popular drug of abuse and is still being encountered regularly by law enforcement. According to National Forensic Laboratory Information System (NFLIS), MDMA reports increased from 2003 through 2009 and steadily decreased from 2009 through the second half of 2013 before leveling off from 2014 to 2016 at 2,901 drug reports representing 0.36% total drug reports from State and local laboratories in the U.S.[2] The data (NFLIS reports) demonstrates that MDMA continues to be trafficked for its psychoactive effects.

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*.[3] MDMA is a powerful recreational drug of abuse resulting in toxic outcomes to serotonin neurons within the cortex and the hippocampus, amongst other areas.[4] The desired effects of MDMA have included increased energy, euphoria, and positive social and emotional feelings. However, accompanying these effects are a host of harms that 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).[5] 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.[6]

Scientific data continue to demonstrate that MDMA is a threat to public health and safety. Acute and long-term adverse health effects are documented for MDMA, a Schedule I controlled substance that has a high potential for abuse due to its pharmacological, hallucinogenic, and stimulant effects. While users of MDMA commonly experience intense euphoria while under the influence of the drug, its chronic usage depletes the neurotransmitters that contribute to these feelings. Neurotransmitter depletion can lead to adverse mental health effects such as depression, anxiety, panic, and psychosis—conditions common to other drugs that are susceptible to abuse. In response to the drug's activity, remodeling and degeneration of brain circuitry have been observed in animal and human studies. Consequently, MDMA users experience long lasting confusion, depression, and neurocognitive impairment. Thus, MDMA has the capacity to cause lasting physical harm to the user (neurological damage) and continues to be a threat to public health and safety.[7]

Current research shows that MDMA, even when taken in low doses, is neurotoxic.[8]

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2 NFLIS, 2016 MIDYEAR REPORT (US. Dept. of Justice, DEA (2016).

3 Commonly Abused Drugs Charts, https://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts#mdma-ecstasy-molly (last visited July 19, 2017).

4 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*, BRAIN 133: 1779-1797 (2010).

5 J Meyer, 3,4-Methylenedioxymethamphetmine (MDMA): current perspectives. SUBSTANCE ABUSE REHABILITATION 4: 83–99 (2013).

6 UD McCann et al., *Positron Emission Tomographic Evidence of Toxic Effect of MDMA ("Ecstasy") on Brain Serotonin Neurons in Human Beings*, LANCET 352: 1433-1437 (1998); RL Cowan, *Neuroimaging Research in Human MDMA Users: a Review*, PSYCHOPHARMACOLOGY 189: 539-556 (2007).

7 AC Parrott et al., *MDMA is Certainly Damaging after 25 Years of Empirical Research: a Reply and Refutation of Doblin*, HUMAN PSYCHOPHARMACOLOGY 29: 109-119 (2014).

8 AC Parrott et al., *MDMA (3,4-methylenedioxymethamphetamine) or ecstasy: the contemporary human and animal research perspective*, J PSYCHOPHARMACOL 143, 143-6 (2006).

Moreover, repeated findings have continued to confirm that MDMA serves as a catalyst for other neurological disorders such as serotonin syndrome and depression.[9] This is concerning given that Ecstasy tablets have notably increased in overall size and the amount of MDMA per tablet. There have also been reported increases in the clandestine manufacturing and trafficking of the substance.[10]

Despite the overwhelming amount of scientific data that underscores the dangers of MDMA, there continues to be a misplaced belief among users and traffickers that the drug is safe and benign, even amidst the many reports of victims suffering from severe acute toxicity and deaths.[11] In fact, MDMA is one of the most popular drugs bought online and on the "darknet," where transactions are intentionally hidden to evade detection.[12] It is misleading and dangerous to send the message to young people that MDMA is a benign drug in response to clinical trials; many other Schedule I controlled substances such as marijuana, psilocybin, and LSD have been or continue to be investigated in humans and have not been approved therapeutic agents. The particular example with MDMA is showcased by a first-hand experience of an individual who decided to use MDMA based upon its use in psychotherapy and showed memory deficits in a neurocognitive study ten years later.[13] In fact, one study found impaired memory and clinically significant levels of depression, impulsiveness, and sleep disturbance in a group of former and current ecstasy users.[14] Still nearly half of high school students surveyed (10th and 12th graders) continue to believe that "molly" (a slang term for a variety of synthetic cathinones including MDMA) is not harmful if they try it once or twice.[15]

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;[16] (2) significantly worse performance of male MDMA users on the tasks that correlate to cognitive flexibility and on the combined executive function task;[17] (3) reduced associative memory performance using fMRI;[18] (4) a significant decrement in

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9 R de la Torre et al. *Human pharmacology of MDMA: pharmacokinetics, metabolism, and Disposition*, THER DRUG MONIT 26: 137 (2004).

10 *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.

11 P Armenian et al., *Multiple MDMA (Ecstasy) Overdoses at a Rave Event: A Case Series*. J INTENSIVE CARE MED May 28 (2012).

12 Findings per DEA investigations.

13 AC Parrott. *MDMA is certainly damaging after 25 years of empirical research: a reply and refutation of Doblin et al.* HUMAN PSYCHOPHARMACOLOGY 29: 109-119 (2014).

14 L Taurah et al. *Depression, impulsiveness, sleep, and memory in past and present polydrug users of 3,4-methylenedioxymethamphetamine (MDMA,ecstasy)*. Psychopharmacology (Berl) Feb;231(4):737-51 (2014).

15 LD Johnston et al., *Monitoring the Future national survey results on drug use, 1975-2016: Overview, key findings on adolescent drug use*. Ann Arbor: Institute for Social Research, The University of Michigan.

16 K Leslie, et al., *Preliminary Evidence of Hippocampal Dysfunction in Adolescent MDMA ("Ecstasy") Users: Possible Relationship to Neurotoxic Effects*, PSYCHOPHARMACOLOGY (Berl) 383, 38390 (2004).

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

18 G Jager et al., *Assessment of Cognitive Brain Function in Ecstasy Users and Contributions of Other Drugs of Abuse: Results from an FMRI Study*, NEUROPSYCHOPHARMACOLOGY 33: 247-258 (2008).

verbal memory in the MDMA user as compared to control subjects;[19] and (5) cortex deficiencies during a word recognition task in MDMA users.[20] Lastly, a study 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 which persisted even after they were abstinent from MDMA use for two years prior to testing.[21]

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 who presented to an emergency room with MDMA toxicity, four who suffered permanent neurological, musculoskeletal and/or renal deficits and two who died, all directly resultant from MDMA ingestion.[22] Other overdose events with MDMA have been reported, some with tragic outcomes.[23]

Studies demonstrate that MDMA dependence is associated with intensity and lifetime use.[24] MDMA-associated overdoses commonly occur with polysubstance use; other drugs are possibly used to enhance the effects of MDMA. In the absence of national data for MDMA overdose deaths, the Florida Department of Law Enforcement publishes the *Drugs in Deceased Persons Report*. From 2006 to 2012, a total of 286 MDMA-related deaths were reported.[25] This remains especially concerning given that, as noted above, the amount of MDMA present in each individual pill has increased in recent years.[26]

In its 2001 Report to Congress, the Sentencing Commission identified 6 major factors that helped guide the decision to use the 500:1 ratio. Those were as follows:

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

20 AP Burgess et al., *Event Related Potential (ERP) Evidence for Selective Impairment of Verbal Recollection in Abstinent Recreational Methylenedioxymethamphetamine ("Ecstasy")/Polydrug Users*, PSYCHOPHARMACOLOGY 216: 545-556 (2011).

21 MJ Morgan et al., *Ecstasy (MDMA): Are the Psychological Problems Associated With Its Use Reversed By Prolonged Abstinence?* PSYCHOPHARMACOLOGY 159: 294-303 (2002).

22 P Armenian et al., *Multiple MDMA (Ecstasy) Overdoses at a Rave Event: A Case Series*, J. INTENSIVE CARE MED. 28: 252-258 (2012).

23 MORBIDITY AND MORTALITY WEEKLY REPORT, ECSTASY OVERDOSES AT A NEW YEAR'S EVE RAVE – LOS ANGELES, CA, 2010 677-681 (Center for Disease Control June 11, 2010); MORBIDITY AND MORTALITY WEEKLY REPORT, ILLNESS AND DEATHS AMONG PERSONS ATTENDING AN ELECTRONIC DANCE MUSIC FESTIVAL – NEW YORK CITY, 2013 1195-98 (Center for Disease Control Dec. 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 242, 242-248 (2004).

24 N Bruno and 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*, DRUG AND ALCOHOL DEPENDENCE 83: 221-235 (2006).

25 After 2012, FDLE changed its reporting so that MDMA was included in a category of hallucinogenic phenethylamines/piperizes and identified as a separate category.

26 EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION, RECENT CHANGES IN EUROPE'S MDMA.ECSTASY MARKET (EMCCDA Rapid communication, Publication Office of the E.U., Luxembourg, April 2016).

1. The rapidly growing incidence of abuse of the controlled substances
2. The threat to public safety that such abuse poses
3. The recent increase in the illegal importation of the controlled substances
4. The young age at which children are beginning to use the controlled substances
5. The fact that the controlled substances are frequently marketed to youth
6. The large number of doses per gram of the controlled substances.[27]

These factors considered by the Commission continue to hold true and have been further strengthened by studies demonstrating the harms associated with MDMA use, the aggressive marketing to youth, and the current importation and trafficking patterns. Continuous publications utilizing updated and more precise measurements repeatedly conclude that MDMA, even when taken in low doses, is neurotoxic.

For the reasons outlined above, the equivalency of 1 gm of MDMA = 500 gm of marijuana should be maintained in response to those traffickers preying on vulnerable populations, especially given our understanding of the drug's negative outcomes on the user.

The USSC was correct in its analysis in 2001, and information gained over the past 16 years has only substantiated that MDMA is harmful, neurotoxic, and potentially lethal to users. The illicit manufacture and distribution of this neurotoxic and potentially lethal substance deserves an appropriate penalty for the harms it is causing to users and society. To be sure, nothing has made the drug less dangerous than it was in 2001.

Issue 2

As noted above, courts have typically identified MDMA as the most closely related controlled substance to methylone. Under the current guidelines, including Application Note 6 to §2D1.1, is this determination appropriate? If not, is there any controlled substance referenced in §2D1.1 that is most closely related to methylone? If so, what substance?

The Commission seeks comment on whether the Commission should provide a marihuana equivalency for methylone. If so, and MDMA is determined to be the most closely related controlled substance to methylone, should the Commission specify a marihuana equivalency for methylone at the same ratio as MDMA, regardless of whether the ratio for MDMA is changed from its current 500:1 level? Should the Commission establish a marihuana equivalency for methylone at a higher or lower ratio than the current MDMA equivalency? If so, what equivalency should the Commission provide and why? To the extent methylone has different characteristics than MDMA, how do those characteristics compare with other controlled substances referenced in §2D1.1 in terms of health effects (including addictiveness and abuse potential), marketing and trafficking patterns, and potency by dosage unit?

If the Commission were to establish a marihuana equivalency for methylone, which is often marketed and consumed in capsule form, should the Commission establish a "typical weight per unit" for methylone in Application Note 9 to §2D1.1?

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27 UNITED STATES SENTENCING COMMISSION, MDMA DRUG OFFENSES: EXPLANATION OF RECENT GUIDELINE AMENDMENTS 3 (2001), https://www.ussc.gov/sites/default/files/pdf/news/congressional-testimony-and-reports/drug-topics/200105_RtC_MDMA_Drug_Offenses.pdf.

Methylone

In law enforcement investigations, it is not uncommon for tablets marketed as "molly" to be composed of synthetic cathinones such as methylone, a drug that shares similar pharmacological effects with MDMA and other substances of abuse such as cocaine. Important health-related issues have emerged in relation to the somatic, psychiatric, and addictive consequences of methylone use. According to the DEA's 2011 report that analyzed mephedrone, methylone, and MDPV and recommended temporary scheduling of these substances under Schedule I, these drugs were "the most commonly encountered synthetic cathinone. . . represent[ing] more than 98% (1,401 of 1,429) of the synthetic cathinones that have been encountered by law enforcement."[28] The report also observed that at the time of its publishing, the abuse of these drugs was growing, with poison control centers receiving 4,137 calls in forty-seven states and the District of Columbia relating to these three specific substances.[29] According to the DEA's 2016 special report (NFLIS, October 2016) on synthetic drugs, from January 2013 through December 2015, the 20 most frequently identified synthetic cathinones accounted for 51,824 drug reports from state and local forensic laboratories.[30] Among these reports, methylone, alpha-PVP, and ethylone accounted for 91% of the 51,824 drug reports. Whereas methylone decreased from 2013 to 2015 for all U.S. census regions, ethylone increased during the same period for all regions.[36]

By way of background, research in anti-depressant and anti-Parkinson agents resulted in the development and patenting of methylone in 1996.[31] However, there is no evidence that methylone has a legitimate non-research use. According to the Department of Health and Human Services (HHS), as of July 2017, 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, improved concentration, and improved focus.[32] The number of deaths associated with the use of this substance highlights the danger to the user

MDMA is considered to be the most closely related substance to methylone; however, the substance also shares similarities with cocaine and other stimulants. Many courts have reached the opinion that methylone is most similar to MDMA in applying §2D1.1 Note 6.[33] This reaffirms our

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28 DRUG ENFORCEMENT ADMINISTRATION, BACKGROUND, DATA AND ANALYSIS OF SYNTHETIC CATHINONES: MEPHEDRONE (4-MMC), METHYLONE (MDMC) AND 3,4-METHYLENEDIOXYPYROVALERONE (MDPV) 4 (Aug. 2011), www.regulations.gov/document?=DEA-2011-0008-0002. The report also notes that "Of all the reports, (1,429) of synthetic cathinones recorded by NFLIS from January 2009 to June 2011, 55% (791) were MDPV, 23% (331) were mephedrone, and 20% (279) were methylone."

29 *Id.* at 11.

30 NFLIS, SPECIAL REPORT: SYNTHETIC CANNABINOIDS AND SYNTHETIC CATHINONES REPORTED IN NFLIS, 2013-2015 (US DOJ DEA Diversion Control Division 2016), https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS-SR-SynthCannabinoidCathinone.pdf..

31 P Jacob and A Shulgin, U.S. Patent No. WO 1996039122 (filed Jun. 6, 1996).

32 L Karila et al., *Synthetic Cathinones: A New Public Health Problem,13(1)* CURRENT NEUROPHARMACOLOGY 12, 12-20 (2015); L Karila et al., *The Effects and Risks Associated to Mephedrone and Methylone in Humans: A Review of the Preliminary Evidences*, 126 BRAIN RES BULL 61, 61-67(2016).

33 See e.g. *United States v. Arroyo*, 2:14-cr-186 (D. N.J.); *United States v. Borges*, 13-cr-20239 (S.D. FL.); *United States v. Flasey*, 12-cr-29 (M.D.FL.); *United States v. Guerrero*, 12-cr-390 (D.N.J.); *United States v. Marhsall*, 1:14-cr-00232 (N.D.N.Y.); *United States v. Martinez*, 13-cr-00316 (E.D.N.Y.)(comparing to MDMA); but see e.g. *United States*

belief that methylone should have the same marijuana equivalency as MDMA.

Scientific Evidence of the Substance's Pharmacological Effect

Methylone has many similarities with MDMA and other Schedule I substances. The clinical presentation of intoxication is similar to MDMA and other substances (*e.g.*, cathinone, methcathinone, MDMA, amphetamine, methamphetamine, and cocaine) that have a stimulant effect on the central nervous system.[34] 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.[35] Furthermore, methylone, like MDMA, has been associated with serotonin syndrome, a syndrome characterized by altered mental status, hyper-reflexia, and autonomic instability and possibly leading to death in extreme cases.[36]

A comprehensive review of the scientific literature suggests that methylone is as potent as MDMA in various animal studies that have investigated methylone's abuse potential. According to these studies (e.g., drug discrimination, self-administration, conditioned place preference, and locomotor activity studies) methylone, similar to MDMA, produces pharmacological effects that are similar to those substances that cause a stimulant effect on the central nervous system. The types of animal abuse-related behavioral pharmacology that may be important in an abuse potential assessment for a central nervous system (CNS)-active drug and that have been recommended by the Department of Health and Human Services (HHS) include drug discrimination, self-administrations, and conditioned place preference studies.[37] In addition, locomotor tests may provide relevant information about the behavioral similarities of a test drug relative to known drugs of abuse.

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v. Carrillo, 13-cr-0779 (C.D. CA); *United States v. Farmer*, 13-cr-20920 (E.D.MI.); *United States v Farrington*, 13-cr-129 (D.ME); *United States v. Letasi*, 13-cr-635 (D.N.J.); *United States v. Marte*, 13-cr-20537(S.D.FL.); *United States v. McLaughlin*, 13-cr-239 (N.D.N.Y.); *United States v. Merlin*, 13-cr-96 (D.NV.); *United States v. Murdough*, 12-cr-163 (D.N.H.); *United States v. Myers*, 13-cr-117 (D.N.H.); *United States v. Orton*, 12-cr-00017 (D.ME.); *United States v. Safari*, 12-cr-249 (E.D.VA.)(believed to be compared to MDMA but applying an interpretation of the guidelines resulting in a 1:250 ratio).

34 L Karila, et al., *Synthetic Cathinones: A New Public Health Problem*, CURRENT NEUROPHARMACOLOGY 13(1)12-20 (2015); L Karila et al., *The Effects and Risks Associated to Mephedrone and Methylone in Humans: A Review of the Preliminary Evidences*, BRAIN RES BULL 126: 61-67 (2016).

35 JM Pearson et al., *Three Fatal Intoxications Due to Methylone*, J. ANALYTICAL TOXICOLOGY 36: 444-451 (2012); B. Warrick et al., *Lethal Serotonin Syndrome After Methylone and Butylone Ingestion*, J. MED. TOXICOLOGY 8: 65-68 (2012); B. Cawrse et al., *Distribution of Methylone in Four Postmortem Cases*, J. ANALYTICAL TOXICOLOGY 36: 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)*, J. MED. TOXICOLOGY 8: 69-75 (2012); K. Kesha et al., *Methylenedioxypyrovalerone ("Bath Salts"), Related Death: Case Report And Review Of The Literature*, J. FORENSIC SCI. 58: 1654-1659 (2013).

36 R de la Torre, et al., *Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition*. THER DRUG MONIT. Apr;26(2):137-44. Review (2004); Warrick BJ et al. *Lethal serotonin syndrome after methylone and butylone ingestion*. JOURNAL OF MEDICAL TOXICOLOGY: OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF MEDICAL TOXICOLOGY 8:65-68 (2012).

37 HHS, U.S. Department of Health and Human Services (HHS), *Assessment of abuse potential of drugs Guidance for industry*. January 2017 available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

The drug discrimination study in animals is a commonly used method to assess the abuse potential of test drugs or substances. This method can be used to predict subjective effects of substances in humans.[38] This is because 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. 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.[39] Data from a separate published drug discrimination study found that methylone (ED_{50} = 2.66 mg/kg) fully substitutes for the discriminative stimulus effects produced by methamphetamine.[40] MDMA, also tested by these authors, fully substitutes for the discriminative stimulus effects produced by methamphetamine with an ED_{50} of 1.83 mg/kg.[41] In rodents trained to discriminate cocaine from saline, methylone substitutes for cocaine with ED_{50} values 1.47 and 3.09 mg/kg, respectively. This is highly relevant, the animal perceives the effects of methylone to be similar to the training drug cocaine. Drug discrimination studies are accepted as the gold standard in studying abuse-related effects of psychoactive drugs.[42] Thus, in drug discrimination studies, methylone is slightly less potent than MDMA in MDMA-trained animals, but slightly more potent than cocaine in cocaine-trained animals.

Another study used to assess the abuse potential or reinforcing effects of novel drugs is the self-administration study. In drug self-administration studies, drugs that have rewarding properties in animals will likely increase the behavioral responses of animals to obtain additional drugs.[43] Furthermore, drugs that have rewarding effects in animals are likely to produce rewarding (*i.e.*, reinforcing) effects in humans, which is indicative of abuse potential.[44] In self-administration studies, methylone, like MDMA, was self-administered by rodents.[45] The conclusion from these

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38 RL Balster and GE Bigelow. *Guidelines and methodological reviews concerning drug abuse liability assessment.* DRUG AND ALCOHOL DEPENDENCE, 70: S13-40 (2003); Panlilio LV, Goldberg SR. *Self-administration of drugs in animals and humans as a model and an investigative tool.* ADDICTION, 102: 1863-1870 (2007); Kamien JB, et al. *Drug discrimination by humans compared to nonhumans: current status and future directions.* PSYCHOPHARMACOLOGY, 111: 259-270 (1993).

39 T Dal Cason et al., *Cathinone: An investigation of several N-alkyl and methylenedioxy-substituted analogs.* PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, 58: 1109-1116 (1997).

40 MB Gatch , CM Taylor, MJ Forster. *Locomotor stimulant and discriminative stimulus effects of 'bath salt' cathinones.* BEHAVIOURAL PHARMACOLOGY, 24: 437-447 (2013).

41 NIDA, National Institute on Drug Abuse, email communication, (2012).

42 CR Schuster and CE Johanson, *Relationship between the discriminative stimulus properties and subjective effects of drugs.* PSYCHOPHARMACOLOGY 161-175 (1988); M Solinas et al., *Using drug-discrimination techniques to study the abuse-related effects of psychoactive drugs in rats.* NATURE PROTOCOLS 1(3): 1194-1206 (2006); LP Carter and RR Griffiths. *Principles of laboratory assessment of drug abuse liability and implications for clinical development.* DRUG ALCOHOL DEPEND S14-S25 (2009).

43 RL Balster and GE Bigelow. *Guidelines and methodological reviews concerning drug abuse liability assessment.* DRUG AND ALCOHOL DEPENDENCE, 70: S13-40 (2003); LV Panlilio and SR Goldberg. *Self-administration of drugs in animals and humans as a model and an investigative tool.* ADDICTION, 102: 1863-1870 (2007).

44 HHS, Department of Health and Human Services. *Basis for the recommendation to place 3,4-methylenedioxymethcathinone (methylone) and its salts in Schedule I of the Controlled Substances Act (CSA).* Dated August 14 (2012).

45 KM Creehan et al., Intravenous self-administration of mephedrone, methylone and MDMA in female rats. Neuropharmacology, 92: 90-97 (2015); LR Watterson et al. *The Reinforcing and Rewarding Effects of Methylone, a*

studies was that methylone may possess an addiction potential similar to or greater than MDMA.

The conditioned place preference (CPP) paradigm is yet another preclinical animal behavioral model used to study the reinforcing effects (rewarding or aversive) of drugs.[46] CPP tests are able to detect addictive substances. Psychostimulants, such as amphetamine and cocaine, often produce a robust CPP. In the conditioned place preference test, mice treated with of methylone (intraperitoneal doses of 2.5 and 5.0 mg/kg) developed CPP confirming that methylone, like methamphetamine, has a rewarding effect.[47]

Stimulant effects can be assessed in locomotor activity studies (i.e., studies of enhanced physical performance). Several studies show that methylone, like methamphetamine and cocaine, is a CNS stimulant.[48] In locomotor activity studies, methylone treatment resulted in time- and dose-dependent stimulation of locomotor activity in doses from 3 to 30 mg/kg. The stimulant effects of methylone (3 and 10 mg/kg) occurred within 10 minutes following injection and lasted 60 to 120 minutes. Based on the 30-minute time period in which maximal stimulant effects occurred (0 to 30 minutes following injection), an ED_{50} of 1.5 mg/kg was calculated. The maximal stimulant effect of methylone was 87% of the maximal stimulant effect of methamphetamine and 82% that of cocaine. In comparison, treatment with methamphetamine resulted in time- and dose-dependent stimulation of locomotor activity following 0.5 to 4 mg/kg with stimulant effects occurring within 10 minutes following injection and lasting 130 to 310 minutes. The ED_{50} of methamphetamine was estimated at 0.48 mg/kg. Treatment with cocaine resulted in time- and dose- dependent stimulation of locomotor activity following 10 to 40 mg/kg with stimulant effects of 10 and 20 mg/kg occurring within 10 minutes following injection and lasting 120 to 170 minutes. The ED_{50} of cocaine was estimated at 7.2 mg/kg. In a similar study investigating the effects of methylone and other synthetic cathinones on locomotor activity, subcutaneous administration of methylone (5 – 25 mg/kg), like MDMA (5 mg/kg), dose-dependently increased locomotor activity in mice.[49] In yet another study, mice that have been given methylone by oral administration, methylone (5 - 100 mg/kg), like MDMA and methamphetamine, significantly increased locomotor activity.[50] The maximum increase in locomotor activity for methylone occurred at 50 mg/kg. In comparing the effects of the methylone, MDMA, and methylone administered to mice at equivalent doses of 0.205 mmol/kg (which is equivalent to 50 mg/kg methylone) on locomotor activity, methylone increased locomotor activity

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Synthetic Cathinone Commonly Found in "Bath Salts" ADDICTION RESEARCH & THERAPY S9:002. doi:10.4172/2155-6105.S9-002 (2012).

46 I Stolerman. Drugs of abuse: behavioral principles, methods and terms. Trends in Pharmacological Sciences, 13: 170-176 (1992); JA Prus et al., *Conditioned Place Preference*. In: Buccafusco JJ, editor. METHODS OF BEHAVIOR ANALYSIS IN NEUROSCIENCE. 2nd edition. Boca Raton (FL): CRC Press; Chapter 4. Available from: http://www.ncbi.nlm.nih.gov/books/NBK5229/ (2009).

47 M Miyazawa et al., *Behavioral and rewarding effects of methylone, an analog of MDMA in mice*. HIROSAKE MEDICAL JOURNAL, 62: 56-71 (2011).

48 MH Baumann et al., *The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue*. NEUROPSYCHOPHARMACOLOGY. 37: 1192-1203 (2011); M Miyazawa, et al., *Behavioral and rewarding effects of methylone, an analog of MDMA in mice*. HIROSAKE MEDICAL JOURNAL, 62: 56-71 (2011); R Lopez-Arnau et al., *Comparative Neuropharmacology Of Three Psychostimulant Cathinone Derivatives: Butylone, Mephedrone and Methylone*. BRIT J PHARMACOLOGY 167: 407-420 (2012).

49 R Lopez-Arnau et al., *Comparative Neuropharmacology Of Three Psychostimulant Cathinone Derivatives: Butylone, Mephedrone and Methylone*. BRIT. J. PHARMACOLOGY 167: 407-420 (2012).

50 M Miyazawa et al. *Behavioral and rewarding effects of methylone, an analog of MDMA in mice*. HIROSAKE MEDICAL JOURNAL, 62: 56-71 (2011).

more than methamphetamine or MDMA. Thus, in locomotor activity studies, methylone, compared to MDMA, induced locomotor activity but to a greater degree.

The above mentioned data indicate that methylone produces pharmacological effects that are similar to those produced by Schedule I and II substances methamphetamine, cocaine, and MDMA. Methylone, like methamphetamine, amphetamine, and cocaine, is a CNS stimulant and produces locomotor stimulant effects in mice.[51] Methylone substitutes for MDMA, cocaine, or amphetamine in rats trained to discriminate MDMA, cocaine, or amphetamine from saline, respectively.[52] Methylone, like methamphetamine, produced rewarding effects as studied in CPP tests.[53] Based on the results of preclinical studies, HHS postulates that in humans, methylone is likely to produce pharmacological effects similar to those produced by amphetamine, methamphetamine, cocaine, and MDMA.[54] Although some animal abuse-related behavioral pharmacology studies show methylone to be less potent than MDMA, others show methylone to be as potent or more potent than MDMA. So collectively, given the variations in these animal studies, it is reasonable to conclude that in humans it is expected that methylone will be at least as potent as MDMA.

The Substance's History and Current Pattern of Abuse

The DEA's forensic laboratories have analyzed drug exhibits received from state, local, and 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 indicates that the most common methods of administering methylone are by swallowing capsules or tablets and by snorting the powder. The reported average amount of use reported for methylone ranged from 100 mg to 250 mg.[55] In contrast, the average amount of MDMA used ranged from 75 mg to 125 mg.[56] Evidence from poison centers, published case reports, and law enforcement encounters suggest that the main users of methylone are young adults.[57] 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

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51 MH Baumann et al. *The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue*. NEUROPSYCHOPHARMACOLOGY. 37: 1192-1203 (2011); M Miyazawa, T Kojima, S Nakaji. *Behavioral and rewarding effects of methylone, an analog of MDMA in mice*. HIROSAKE MEDICAL JOURNAL 62: 56-71 (2011); R Lopez-Arnau et al., *Comparative Neuropharmacology of Three Psychostimulant Cathinone Derivatives: Butylone, Mephedrone and Methylone*. BRIT. J. PHARMACOLOGY 407:407-420 (2012).

52 T Dal Cason et al., *Cathinone: An investigation of several N-alkyl and methylenedioxy-substituted analogs*. PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, 58: 1109-1116 (1997); Gatch MB, et al. *Locomotor stimulant and discriminative stimulus effects of 'bath salt' cathinones*. BEHAVIOURAL PHARMACOLOGY, 24: 437-447 (2013).

53 M Miyazawa et al. *Behavioral and rewarding effects of methylone, an analog of MDMA in mice*. HIROSAKE MEDICAL JOURNAL, 62: 56-71 (2011).

54 HHS 8-factor review and scheduling recommendation for methylone, available at https://www.regulations.gov/document?D=DEA-2012-0006-0002 (2014).

55 JP Kelly et al., *Cathinone Derivatives: a Review of Their Chemistry, Pharmacology, Toxicology*, DRUG TESTING AND ANALYSIS 3: 439-453 (2011).

56 J Cami et al., *Human Pharmacology of 3,4-Methylenedioxymethamphetamine ("Ecstasy"): Psychomotor, Performance and Subjective Effects*, J. CLINICAL PSYCHOPHARMACOLOGY 20: 455-466 (2000); AC Parrott, *Human Psychobiology of MDMA or 'Ecstasy': an Overview of 25 Years of Empirical research*, HUMAN PSYCHOPHARMACOLOGY 28: 289-307 (2013).

57 DRUG ENFORCEMENT ADMINISTRATION, BACKGROUND, DATA AND ANALYSIS OF SYNTHETIC CATHINONES: MEPHEDRONE (4-MMC), METHYLONE (MDMC) AND 3,4-METHYLENEDIOXYPYROVALERONE (MDPV) (Aug. 2011), www.regulations.gov/document?=DEA-2011-0008-0002.

were sold as MDMA (marketed as "Molly") were found by the DEA to contain methylone.[58]

Equivalency for Methylone: Methylone as Comparable to MDMA

Regarding the methylone equivalency, the DEA proposes that the Commission compare Methylone to MDMA. Based on the evidence that methylone has similarities with MDMA regarding its pharmacological and toxic potential.[59] the DEA recommends that the marijuana equivalency for methylone be the same as for MDMA (1:500 marijuana). If the Commission should consider an equivalency greater than 1:500 based upon the established abuse liability and similarities with additional drugs of abuse, the DEA would be in full support.

Issue 3

The Commission seeks general comment on whether there are synthetic cathinones, other than methylone, that are substantially similar in their effects to MDMA. If so, what are those substances? How do those substances compare to MDMA in terms of health effects (including addictiveness and abuse potential), marketing and trafficking patterns, and potency by dosage unit? If the Commission were to include any such other synthetic cathinones in the Drug Equivalency Tables at Application Note 8(D) to §2D1.1, how should the Commission establish marihuana equivalencies for these other synthetic cathinones in relation to one another and to the other controlled substances referenced in §2D1.1?

Last year the DEA and the Department of Justice requested the Commission to create equivalencies in the guidelines for both *Mephedrone* and *MDPV*.[60] The DEA renews that request.

Synthetic Cathinones

Methylone, mephedrone, and MDPV are synthetic cathinones that have many similarities to other Schedule I substances such as cathinone, methcathinone, and MDMA. 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.[61] 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.[62]

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58 *Id.* at 34.

59 DRUG ENFORCEMENT ADMINISTRATION, SCHEDULE OF CONTROLLED SUBSTANCE: PLACEMENT OF 3,4-METHYLENEDIOXY-N-METHYLCATHINONE (METHYLONE) INTO SCHEDULE I: BACKGROUND, DATA, AND ANALYSIS: EIGHT FACTORS DETERMINATIVE OF CONTROL AND FINDINGS PURSUANT TO 21 U.S.C. 812(B) (2012).

60 *See* JONATHAN WROBLEWSKI, DIRECTOR, OFFICE OF POLICY AND LEGISLATION, CRIMINAL DIVISION, DEP'T OF JUSTICE, ANNUAL LETTER TO PATTI B. SARIS, CHAIR, U.S. SENTENCING COMM'N.(2014), http://www.ussc.gov/sites/default/files/pdf/amendment-process/public-comment/20140729/DOJ.pdf).

61 JM Prosser and LS Nelson, *The Toxicology of Bath Salts: A Review of Synthetic Cathinones*, J. MEDICAL TOXICOLOGY 8: 33-42 (2012).

62 JM Pearson et al., *Three Fatal Intoxications Due to Methylone*, J. ANALYTICAL TOXICOLOGY 36: 444-451 (2012); B. Warrick et al., *Lethal Serotonin Syndrome After Methylone and Butylone Ingestion*, J. MED. TOXICOLOGY 8: 65-68 (2012); B. Cawrse et al., *Distribution of Methylone in Four Postmortem Cases*, J ANALYTICAL TOXICOLOGY 36 :434-439 (2012); J Wyman et al., *Postmortem Tissue Distribution of MDPV Following Lethal Intoxication by "Bath Salts,"* J ANALYTICAL TOXICOLOGY 37: 182-185 (2013); B Murray et al., *Death Following Recreational Use Of Designer Drug*

The DEA has encountered these synthetic cathinones being trafficked for their psychoactive properties with no regard for the user's safety. These substances are falsely marketed as "research chemicals," "plant food or fertilizer," "jewelry cleaner," "stain remover," "insect repellant," or "bath salts" to evade detection. 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 were promoted as "legal" alternatives to cocaine, methamphetamine, and MDMA, because at the time, detection of these substances was not included in the routine drug screen for illicit substances.

On October 21, 2011, the DEA Administrator 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 posed an imminent threat to public safety.[63] The Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) (FDASIA) 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.

The Public Health Concerns of MDPV and Mephedrone

Adverse health effects associated with the consumption of 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.[64] Excited delirium, a condition characterized by agitation, aggression, acute distress and sudden death,[65] is also associated with MDPV.

The DEA remains concerned about these psychoactive substances because of their composition of highly dangerous substances that elicit serious and even lethal outcomes. This danger, coupled with easy access, has made them responsible for a large number of hospital emergency department admissions and Medical Examiner reports.[66]

Why Equivalencies are Necessary for These Specific Synthetics

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"Bath Salts" Containing 3,4-Methylenedioxypyrovalerone (MDPV), J MED TOXICOLOGY 8: 69-75 (2012); K Kesha et al., *Methylenedioxypyrovalerone ("Bath Salts"), Related Death: Case Report And Review Of The Literature*, J FORENSIC SCI 58: 1654-1659 (2013).

63 76 Fed. Reg. 65371 (Oct. 21, 2011).

64 JM Pearson et al., *Three Fatal Intoxications Due to Methylone*, J. ANALYTICAL TOXICOLOGY 36:444-451 (2012); B Warrick et al., *Lethal Serotonin Syndrome After Methylone And Butylone Ingestion*, J. MED. TOXICOLOGY8:65-68 (2012); B Cawtse et al., *Distribution of Methylone in Four Postmortem Cases*, J. OF ANALYTICAL TOXICOLOGY, 36:434-439 (2012); J Wyman et al., *Postmortem Tissue Distribution of MDPV Following Lethal Intoxication by "Bath Salts,"* J. OF ANALYTICAL TOXICOLOGY 37: 182-185 (2013); B. Murray et. al., *Death Following Recreational Use Of Designer Drug "Bath Salts" Containing 3,4-Methylenedioxypyrovalerone (MDPV)*, J MED. TOXICOLOGY , 8:69-75 (2012); K Kesha et al., *Methylenedioxypyrovalerone ("Bath Salts"), Related Death: Case Report And Review Of The Literature*, J OF FORENSIC SCI 58: 1654-1659 (2013).

65 A Takeuchi et al., *Excited Delirium*, WEST J EMERG. MED 12(1):77-83 (2011).

66 *Deadly Synthetic Drugs: The Need to Stay Ahead of the Poison Peddlers Before the Sen. Comm. On the Judiciary*, 114th Cong. 2 (2016) [hereinafter *Deadly Synthetic Drugs*] (testimony of Dr. Douglass Throckmorton, Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research, Food and Drug Administration NY).

As described below, Mephedrone and Methylone are similar to MDMA and the Commission should use the same marijuana equivalencies for these as MDMA. As explained in Dr. Boos' statement for the March 2017 hearing before the Commission, MDPV is especially comparable to methamphetamine based on the numerous pharmacological studies published in the scientific literature. These studies use accepted methodologies and have been conducted by the leaders in the field of drug abuse research.

According to the DEA's 2011 report analyzing mephedrone, methylone, and MDPV and recommending temporary scheduling under schedule I, these drugs were "the most commonly encountered synthetic cathinone. . . represent[ing] more than 98% (1,401 of 1,429) of the synthetic cathinones that have been encountered by law enforcement."[67] The report also observed that at the time of its publishing, the abuse of these drugs was growing, with poison control centers receiving 4,137 calls in forty-seven states and the District of Columbia relating to these three specific products.[68]

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.[69] There is no evidence that 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.[70]

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. This data 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.[71] 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

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67 DRUG ENFORCEMENT ADMINISTRATION, BACKGROUND, DATA AND ANALYSIS OF SYNTHETIC CATHINONES: MEPHEDRONE (4-MMC), METHYLONE (MDMC) AND 3,4-METHYLENEDIOXYPYROVALERONE (MDPV) 4 (Aug. 2011), www.regulations.gov/document?=DEA-2011-0008-0002. The report also notes that "Of all the reports, (1,429) of synthetic cathinones recorded by NFLIS from January 2009 to June 2011, 55% (791) were MDPV, 23% (331) were mephedrone, and 20% (279) were methylone."

68 *Id.* at 11.

69 L Karila et al., *The Effects and Risks Associated to Mephedrone and Methylone in Humans: A Review of the Preliminary Evidences*, BRAIN RES BULL. 126: 61-67 (2016).

70 L Karila et al., *Synthetic Cathinones: A New Public Health Problem.,13(1)* CURRENT NEUROPHARMACOLOGY 12, 12-20 (2015).

71 College on Problems of Drug Dependence (CPDD) 77th Annual Scientific Meeting, Arizona Biltmore, Phoenix, Arizona, June 13-18, 2015.

and VESSPA questionnaire).[72] Based on the above study, mephedrone has a stimulant effect that is similar to MDMA but less potent. However, these conclusions are made with limitations since there were few participants 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.[73] 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.[74] 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.[75] In an additional study that claims MDMA-like drugs can be discerned from methamphetamine-like drugs by measuring a specific locomotor activity (voluntary wheel activity), mephedrone is more similar to MDMA than to MDPV or methamphetamine.[76]

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.[77] Data from a published drug

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72 *Id.*

73 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).

74 MH Baumann et al., *The Designer Methcathinone Analogs, Mephedrone and Methylone, are Substrates for Monoamine Transporters*, 37 NEUROPSYCHOPHARMACOLOGY 1192, 1192-1203 (2012).

75 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).

76 P-K Huang et al., *Contrasting Effects of d-Methamphetamine,3,4-Methylenedioxymethamphetamine, 3,4-Methylenedioxypyrovalerone, and 4-Methylmethcathinone on Wheel Activity in Rats*, DRUG AND ALCOHOL DEPENDENCE 126: 168-175 (2012).

77 JB Kamien et al., *Drug Discrimination by Humans Compared to Nonhumans: Current Status and Future Directions*, PSYCHOPHARMACOLOGY 11(3): 259-270 (1993); RL Balster & GE Bigelow, *Guidelines and Methodological Reviews Concerning Drug Abuse Liability Assessment*, DRUG AND ALCOHOL DEPENDENCE 70(3):S13-S40 (2003); LV Panlilio & SR Goldberg, *Self-Administration of Drugs in Animal and Humans as a Model and an Investigative Tool*, ADDICTION 102(12): 1863-1870 (2007).

discrimination study indicate that MDMA fully substitutes for the discriminative stimulus effects produced by mephedrone (ED_{50}=0.90 mg/kg) in rats.[78] 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.[79] 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.[80] It has also been reported that mephedrone is used in binges; in other words, the user has a strong desire to re-dose the drug. The desire to re-dose is similar to other reinforcing drugs of abuse. Abusers have reported that typical sessions using mephedrone last approximately 10.4 hours with some individuals administering several times throughout a session.[81] A possible reason for binging may be to prolong the duration of effects. In comparison, the average amount of MDMA used ranged from 75 mg to 125 mg (oral administration).[82] 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.[83]

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.[84] 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.[85] Participants in a survey of

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78 KJ Varner et al., *Comparison of the Behavioral and Cardiovascular Effects of Mephedrone with Other Drugs of Abuse in Rats*, PSYCHOPHARMACOLOGY 225(3):675-685 (2013).

79 JP Kelly et al., *Cathinone Derivatives: a Review of Their Chemistry, Pharmacology, Toxicology*, DRUG TESTING AND ANALYSIS 3: 439-453 (2011).

80 JP Kelly et al., *Cathinone Derivatives: a Review of Their Chemistry, Pharmacology, Toxicology*, DRUG TESTING AND ANALYSIS 3: 439-453 (2011).

81 Schifano et al., *Mephedrone (4-methylmethcathinone: 'meow meow'): chemical, pharmacological and clinical issues.* PSYCHOPHARMACOLOGY(Berl) 214(3):593-602 (2011).

82 AC Parrott, *Human Psychobiology of MDMA or 'Ecstasy': an Overview of 25 Years of Empirical Research*, HUMAN PSYCHOPHARMACOLOGY 28: 289-307 (2013).

83 DEA 3-Factor Analysis Mephedrone, Methylone, and MDPV, October 2011

84 H Uosukainen et al., *Self-reported prevalence of dependence of MDMA compared to cocaine, mephedrone and ketamine among a sample of recreational poly-drug users.* INT J DRUG POLICY 26(1):78-83(2015); M Kapitany-Foveny et al, *Is there any difference in patterns of use and psychiatric symptom status between injectors and non-injectors of mephedrone?* HUM PSYCHOPHARMACOL 30(4): 233-43(2015);

85 76 Fed. Reg. 65371 (Oct. 21, 2011).

readers of a popular UK dance music magazine reported that mephedrone gave a better high than cocaine.[86] 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.[87] 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; while, other products were found to contain mephedrone. The unsuspecting user is at the mercy of the trafficker distributing these dangerous drugs.

Methylenedioxypyrovalerone (MDPV)

Methylenedioxypyrovalerone (MDPV) is closely related in structure and pharmacological effect to the phenethylamines such as the Schedule I and II substances methamphetamine, cathinone, methcathinone, and methylenedioxymethamphetamine (MDMA).[88] MDPV is also structurally related to pyrovalerone, which is a psychoactive drug that was used to treat chronic lethargy and fatigue and at one time was an approved treatment agent.[89] In our assessment, 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.[90]

Scientific Evidence of the Drug's Pharmacological Effects

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.[91] In addition, MDPV is a powerful locomotor stimulant like methamphetamine.[92] As described in the literature, MDPV is at least 10 times more potent than

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86 A Winstock et al., *Mephedrone, new kid for the chop?* ADDICTION 106(1):154-61 (2011).

87 RL Carhart-Harris et al., *A web-based survey on mephedrone* DRUG AND ALCOHOL DEPENDENCE 118: 19-22.

88 CL German, et al., *Bath salts and synthetic cathinones: An emerging designer drug phenomenon*, LIFE SCI. 97:, 2-8 (2014); LJ De Felice, et al., *Synthetic cathinones: Chemical phylogeny, physiology, and neuropharmacology*, LIFE SCI 97: 20-6 (2014).

89 S Strano-Rossi,et al., *Toxicological determination and in vitro metabolism of the designer drug methylenedioxypyrovalerone (MDPV) by gas chromatography/mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry: Rapid communications in mass spectrometry*, RCM 24: 2706-2714 (2010).

90 JM Prosser and LS Nelson, *The Toxicology of Bath Salts: A Review of Synthetic Cathinones*, J. MEDICAL TOXICOLOGY 8: 33-42 (2012).

91 P-K Huang et al., *Contrasting Effects of d-Methamphetamine,3,4-Methylenedioxymethamphetamine, 3,4-Methylenedioxypyrovalerone, and 4-Methylmethcathinone on Wheel Activity in Rats*, DRUG AND ALCOHOL DEPENDENCE 126(1): 168-175 (2012).

92 MH Baumann et al., *Powerful Cocaine-like Actions of 3,4-Methylenedioxypyrovalerone (MDPV), a Principal Constituent of Psychoactive 'Bath Salt' Products*, NEUROPSYCHOPHARMACOLOGY 38(4):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*, NEUROPSYCHOPHARMACOLOGY 38(4): 563-573

cocaine in locomotor studies.[93]

Drug discrimination studies indicate that MDPV produces pharmacological effects that are similar to those of methamphetamine and cocaine.[94] 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.[95] 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.[96] 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.[97] 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. In studies of MDPV self-administered in rats, rats were observed to self-administer a greater and greater amount of MDPV. As a result, the authors of these studies concluded that MDPV poses a substantial threat for compulsive use that is potentially greater than that for methamphetamine.[98]

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

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(2013); M Gatch et al., *Locomotor Stimulant and Discriminative Stimulus Effects of 'Bath Salt' Cathinones*, BEHAVIORAL PHARMACOLOGY 24: 437-447 (2013); JA Marusich et al., *Pharmacology of Novel Synthetic Stimulants Structurally Related to "Bath Salts" Constituents 3,4-Methylenedioxypyrovalerone (MDPV)*, NEUROPHARMACOLOGY 87:206-213 (2014).

93 M Baumann, et al., *Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive 'bath salts' products*. NEUROPSYCHOPHARMACOLOGY, *38*;552-562,(**2013).**

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

95 RI Balster and GE Bigelow, *Guidelines and Methodological Reviews Concerning Drug Abuse Liability Assessment*, DRUG AND ALCOHOL DEPENDENCE 13, 13-40 (2003); LV Panllio & SR Goldberg, *Self-Administration of Drugs in Animals and Humans as a Model and an Investigative Tool*, ADDICTION 102(12) 1863-1870 (2007).

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

97 WE Fantegrossi et al., *In Vivo Effects of Abused 'Bath Salt' Constituent 3,4-Methylenedioxypyrovalerone (MDPV) in Mice: Drug Discrimination, Thermoregulation, and Locomotor Activity*, NEUROPSYCHOPHARMACOLOGY 38(4):563-573 (2013).

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

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 – 2 grams) depending on the substance, duration of intake, and method of administration.[99] 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.[100] 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, Customs and Border Protection (CBP) reports large seizures of MDPV.[101]

Risk to Public Health

MDPV has been reported to cause a number of stimulant-like adverse health effects.[102] 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.[103] 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.[104] Published case reports describing MDPV related adverse effects are summarized below.

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99 P Deluca et al., Psychonaut WebMapping Research Group. 2010. MDPV report, Institute of Psychiatry, King's College London: London, UK; IVERSON, ADVISORY COUNCIL ON THE MISUSE OF DRUGS, CONSIDERATION OF THE CATHINONES, (Mar. 31, 2010).

100 CC Cruickshank and KR Dyer, *A Review of the Clinical Pharmacology of Methamphetamine*, ADDICTION 104(7):1085-1099 (2009).

101 Communications to DEA.

102 GT Collins et al., *Discriminative Stimulus Effects of Binary Drug Mixtures: Studies with Cocaine, MDPV, and Caffeine*. J PHARMACOL EXP THER 359(1):1-10 (2016); LR Watterson et al., *Sensitization to the motor stimulant effects of 3,4-methylenedioxypyrovalerone (MDPV) and cross-sensitization to methamphetamine in rats*. J DRUG ALCOHOL RES 1-21 (2016); P-K Huang et al., *Contrasting effects of d-methamphetamine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxypyrovalerone, and 4-methylmethcathinone on wheel activity in rats*, DRUG AND ALCOHOL DEPENDENCE 168, 168-175 (2012).

103 Glennon RA, *Bath salts, mephedrone, and methylenedioxypyrovalerone as emerging illicit drugs that will need targeted therapeutic intervention*. ADV PHARMACOL 69:581-620 (2014); LM Colon-Perez et al.,*The Psychoactive Designer Drug and Bath Salt Constituent MDPV Causes Widespread Disruption of Brain Functional Connectivity*. NEUROPSYCHOPHARMACOLOGY 41(9):2352-2365(2016).

104 Froberg et al., *Acute Methylenedioxypyrovalerone Toxicity*. J MED TOXICOL 11(2): 185-194; Ross et al., *Psychoactive "bath salts" intoxication with methylenedioxypyrovalerone*. AM J MED 125(9): 854-8.

Regarding MDPV, the DEA recommends that the Commission begin with the marijuana equivalency currently used for methcathinone which has a marijuana equivalency ratio of 1:380, but then impose a ratio for MDPV that is based upon the currently available scientific information and harms to the public, which are more similar to those of methamphetamine as explained above and in various studies.[105] Based on 1) pharmacological similarities between MDPV and methamphetamine, 2) the potency of MDPV relative to methamphetamine, and 3) the marijuana equivalencies for methamphetamine, the DEA recommends the marijuana equivalency of 1000 grams of marijuana for MDPV and for products containing MDPV; a higher equivalency could be justified based upon similarities with methamphetamine.

* * *

We appreciate the opportunity to provide the Commission with our views, comments, and suggestions, and we look forward to working with the Commission on the above projects and proposals, among other things, over the remainder of the amendment cycle. The DEA would also express its desire for a class-based approach to synthetic drugs. The current process is unwieldy and inefficient. The DEA looks forward to working with the Commission to develop a more effective process.

Sincerely,

Demetra Ashley
Acting Assistant Administrator

cc: Commissioners
Ken Cohen, Staff Director
Kathleen Grilli, General Counsel

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105 P-K Huang, et al., *Contrasting effects of d-methamphetamine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxypyrovalerone, and 4-methylmethcathinone on wheel activity in rats*, DRUG AND ALCOHOL DEPENDENCE 126: 168-175 (2012); MH Baumann et al., *Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive 'bath salts' products*, NEUROPSYCHOPHARMACOLOGY 38:552-562 (2013); WE Fantagrossi et al., *In vivo effects of abused 'bath salt' constituent 3,4-methylenedioxypyrovalerone (MDPV) in mice: drug discrimination, thermoregulation, and locomotor activity*, NEUROPHARMACOLOGY 38:563- 573 (2013); MB Gatch et al., *Locomotor stimulant and discriminative stimulus effects of 'bath salt' cathinones*, BEHAVIOURAL PHARMACOLOGY 24:437-447 (2013); JA Marusich et al., *Pharmacology of novel synthetic stimulants structurally related to the "bath salts" constituent 3,4-methylenedioxypyrovalerone (MDPV)*, NEUROPHARMACOLOGY 87:206-213 (2014).