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BEFORE THE
UNITED STATES SENTENCING COMMISSION

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HEARING ON
SENTENCING POLICY FOR SYNTHETIC DRUGS

- - -

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Introduction

New Psychoactive Substances (NPS) are substances trafficked as alternatives to well-studied controlled substances of abuse. NPS have demonstrated adverse health effects such as paranoia, psychosis, and seizures to name a few. Cathinones, cannabinoids, and fentanyl-related substances are the most common NPS drug classes encountered on the illicit drug market, all with negative consequences for the user to include serious injury and death. Our early experience saw substances being introduced from past research efforts in an attempt to evade controls. This has evolved to NPS manufacturers structurally altering substances at a rapid pace with unknown outcomes to targeting specific user populations. These substances represent an unprecedented level of diversity and consequences. Due to clandestine manufacture and unscrupulous trafficking, the user is at great risk. A misconception exists that these substances carry a lower risk of harm In reality, published reports from law enforcement, emergency room physicians and scientists, accompanied with autopsies from medical examiners, have clearly demonstrated the harmful and potentially deadly consequences of using synthetic cathinones.

These substances are introduced in an attempt to circumvent drug controls and the recent flood of NPS remains a challenge for law enforcement and public health. The United Nations Office on Drugs and Crime reported over 700 NPS encountered.[1] The manufacturers and traffickers make minor changes in the chemical structure of known substances of abuse and maintain the pharmacological effect. The trafficking of these new substances of abuse may be in violation of the Controlled Substances Act and Controlled Substances Analogue Enforcement Act. Sometimes violations of the Analogue Act require testimony in court. In addition to investigating the manufacturers and traffickers of drugs of abuse, the Drug Enforcement Administration's (DEA) scientific staff may be called upon to provide testimony at both trial and sentencing.

Background

There has been a dramatic increase in trafficking and abuse of synthetic cathinones since mid-2000. The DEA is utilizing all available tools in response, yet challenges remain in prioritizing the most harmful and persistent substances. The DEA has responded with numerous temporary and permanent scheduling actions to protect the public. The significance of a response is heightened by the rapid appearance and flood of new substances. The user is at risk of serious adverse medical consequences including addiction and death. Responding to the trafficking in synthetic cathinones remains a priority for the DEA. DEA continues to investigate and disrupt synthetic cathinone traffickers.

The psychostimulants synthetic cathinones are marked by serious medical outcomes. The use and abuse of synthetic cathinones is documented by adverse biological, behavioral, medical, and social consequences. Case reports and communications indicate that synthetic cathinones are highly toxic and the adverse health effects include significant sympathomimetic effects, as well as psychosis, agitation, aggression, and sometimes violent and bizarre behaviors such as

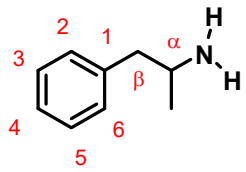
[1] United Nations Office on Drugs and Crime, *World Drug Report 2017* (ISBN: 978-92-1-148291-1, eISBN: 978-92-1-060623-3, United Nations publication, Sales No. E.17.XI.6).

episodes of delirium with persecution. Emergency departments have played a critical role in assisting with complications associated with synthetic cathinone abuse.[2]

Cathinones describe a structural class of substances that share pharmacological effects. These compounds are easy to prepare and can be chemically fashioned in a myriad of ways to produce stimulants (amphetamine-like), stimulant-like hallucinogens or "entactogens."[3] Cathinones have been disguised in designer drug products and marketed as "bath salts," "plant food," "insect repellent," "stain removers," and so on to either disguise and/or entice the user to consume the product. Of significant concern, the unsuspecting user may not be informed as to the substance being consumed or the possible dangers.

Cathinone Structural Class

Cathinone is very similar in chemical structure to amphetamine (1-phenylpropan-2-amine). The two substances differ by only the presence of an oxygen atom at the β-position. This β-position oxygen is referred to as a ketone and cathinones are routinely referred to as beta-ketone (bk) amphetamines. The ketone (C=O) group structurally distinguishes these substances from their amphetamine counterparts. This structural class is well-established and accepted in the scientific literature.[4] Figure 1 depicts the chemical structure for amphetamine noting in red the positions for substitution and the chemical structure for cathinone also noting the positions for substitution.



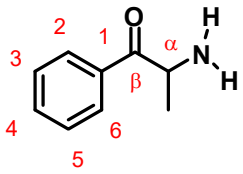


Figure 1. **Amphetamine** **Cathinone**

Cathinone is a stimulant alkaloid found in the leaves of the khat (*Catha Edulis)* plant. Modifications to cathinone's chemical structure give a host of synthetic cathinones. The chemical structure of cathinone (2-amino-1-phenyl propanone) (cathinone) can be altered to produce a series of different compounds which are structurally related to cathinone and are known as synthetic cathinones. There are three primary sites for modification and/or substitution, the phenyl ring, side chain, and nitrogen atom alone or in combination gives a number of

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[2] Emergency Department Visits after Use of a Drug Sold as "Bath Salts" — Michigan, November 13, 2010–March 31, 2011. *MMWR Morb Mortal Wkly Rep* 2011, 60:624-7.

[3] Madras BK (2013). Designer drugs: an escalating public health challenge. *Journal of Global Drug Policy and Practice download at http://globaldrugpolicy.org/Issues/Vol%206%20Issue%203/Designer%20Drugs%20FINAL%20V6%20formatted.pdf*

[4] United Nations Office on Drugs and Crime, The Challenge of New Psychoactive Substances. Global Smart Program, March 2013; JP Kelly. Cathinone Derivatives: A Review of their Chemistry, Pharmacology, and Toxicology. *Drug Testing Analysis* 2011, 3:439-453; M Capriola. Synthetic cathinones. *Clinical Pharmacology: Advances and Applications* 2013, 5:109-115.

synthetic cathinones. Figure 2 notes the various sites on the chemical structure for substitution to give a wide range of synthetic cathinones.

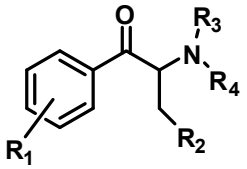


Figure 2. Cathinone with sites for substitution.

With the synthesis of methcathinone being first reported in the scientific literature in 1928[5], many derivatives of the substances have since been prepared and studied in research. The simple synthesis of these substances is reported in the scientific and patent literature. Synthetic cathinones are described as belonging to clusters based upon the pattern of substitutions.[6] Four primary sites of substitution on the cathinone chemical structure are noted above (R_1, R_2, R_3, and R_4). R_1 represents the general substitution on the phenyl ring. For example, the addition of a methyl ($-CH_3$) group to the phenyl ring at the 4 position and the nitrogen (N) atom at R_3 and R_2 and R_4 with a hydrogen (H) atom gives mephedrone. Ring substitution with a methylenedioxy ($-O-CH_2-O-$) group gives a host of cathinones. One of the most prominent is methylone: R_1 is substituted on the phenyl ring with a methylenedioxy group at the 3 and 4 positions and R_3 with a methyl group. The R_2 position is generally substituted with alkyl groups, carbon chains. The addition of ethyl ($-CH_2CH_3$) group at R_2 and a methyl group at R_3 gives pentedrone. R_3 and R_4 represent possible substitutions on the nitrogen (N) atom. The nitrogen atom can be substituted with one group or two and both R_3 and R_4 may be part of a ring structure such as, a pyrrolidine. Substitution of R_2 with an ethyl ($-CH_2CH_3$) group and the R_3 and R_4 with a tetramethylene ($-CH_2CH_2CH_2CH_2-$) moiety forms a pyrrolidine ring. Figure 3 highlights the modifications to cathinone to give the substances detailed above.

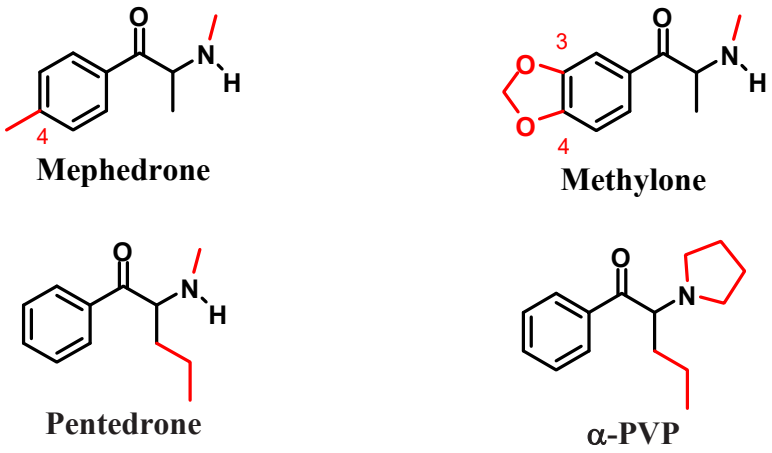


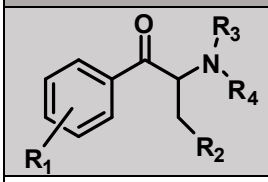
Figure 3. Cathinone structures with specific substitutions

[5] JF Hyde, E Browning, and R Adams. Synthetic homologs of d,l-ephedrine. *Journal of the American Chemical Society* 1928, 50(8):2287–2292.

[6] JP Kelly. Cathinone derivatives: a review of their chemistry, pharmacology, and toxicology. *Drug Testing Analysis* 2011, 3:439-453.

The close structural similarity of the cathinones appearing in response to regulatory controls demonstrates the scientific and patent literature is being trolled for potent substances within a drug class. The synthesis of these substances is practical and precursors are readily available.[7] Clandestine laboratories have readily adapted to regulatory controls and Table 1 details select examples of substances the DEA Drug and Chemical Evaluation Section's scientists have provided opinions and/or testimony for consideration under section 2D.1.1, Note 6 and/or the DEA has controlled. Efforts are routinely duplicated by the scientific staff collecting and evaluating substances for control and providing expert testimony. It is common for the staff to be called upon to provide expert testimony at an analogue trial and at the sentencing hearing for the same case. The table does not provide a complete list of all cathinones encountered or possible. Many structural variations remain possible and based on historical trends it is anticipated new cathinones will be encountered. Therefore, the criteria established by United States Sentencing Commission will be utilized to identify the appropriate comparison under the USSG.

Table 1. Select Chemical Structures for Synthetic Cathinones

	R_1	R_2	R_3	R_4
Cathinone	H	H	H	H
Methcathinone	H	H	methyl	H
Mephedrone	4-methyl	H	methyl	H
4-Methyl-ethcathinone	4-methyl	H	ethyl	H
Pentedrone	H	ethyl	methyl	H
Methylone	3,4-methylenedioxy	H	methyl	H
Dimethylone	3,4-methylenedioxy	H	methyl	methyl
Ethylone	3,4-methylenedioxy	H	ethyl	H
Butylone	3,4-methylenedioxy	methyl	methyl	H
Dibutylone	3,4-methylenedioxy	methyl	methyl	methyl
Pentylone	3,4-methylenedioxy	ethyl	methyl	H
***N*-Ethyl pentylone**	3,4-methylenedioxy	ethyl	ethyl	H
3-Fluoro-methcathinone	3-F	H	methyl	H

[7] M Collins. Some new psychoactive substances: precursor chemicals and synthesis-driven end-products. *Drug Testing and Analysis* 2011, 3:404-416.

4-Fluoro-methcathinone	4-F	H	methyl	H
α-PBP	H	methyl	pyrrolidinyl	
4-Methyl-alpha-pyrrolidinopropiophenone	4-methyl	H	pyrrolidinyl	
α-PVP	H	ethyl	pyrrolidinyl	
MDPV	3,4-methylenedioxy	ethyl	pyrrolidinyl	
Naphyrone	benzyl	ethyl	pyrrolidinyl	

Although many of these substances are being encountered and have been scheduled under the Controlled Substances Act, methcathinone is the only synthetic cathinone listed under the United States Sentencing Guidelines (USSG); MDMA and MDEA, have also been used as comparatives for certain cathinones, consistent with USSG 2D1.1, Application Note 6.

Pharmacological Effects

These substances possess stimulant and/or hallucinogenic properties and the substitutions on the core structure impart these pharmacological effects to varying degrees. For example, a synthetic cathinone can be both methamphetamine-like and MDMA-like in its pharmacological effects.

Due to the similarity in chemical structures and sharing of some common mechanisms of actions with known stimulant drugs of abuse such as MDMA, methamphetamine, and methcathinone, cathinones will share some similarities with these substances in regard to their abuse potential.[8] Available published scientific studies demonstrate that synthetic cathinones (including methcathinone), like cocaine, MDMA and methamphetamine affect monoamine neurotransmission through interactions at monoamine transporters by promoting the release of monoamines (dopamine, serotonin, or norepinephrine) or blocking their uptake.[9,10] Enhanced

[8] MB Gatch, MA Rutledge, and MJ Forster. Discriminative and locomotor effects of five synthetic cathinones in rats and mice. *Psychopharmacology* 2015, 232: 1197-1205.

[9] RA Glennon and M Dukat. Synthetic cathinones: a brief overview of overviews with applications to the forensic sciences. *Annals of Forensic Research and Analysis* 2017, 4(2):1040; L Karila and M Reynaud. GHB and synthetic cathinones: clinical effects and potential consequences. *Drug Testing and Analysis* 2010, 3: 552-559; J Kelly. Cathinone derivatives: A review of their chemistry, pharmacology and toxicology. *Drug Testing and Analysis* 2011, 3: 439-453; MH Baumann, MA Ayestas, JS Partilla, JR Sink, AT Shulgin, PF Daley, SD Brandt, RB Rothman, AE Ruoho and NV Cozzi. The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. *Neuropsychopharmacology* 2012, 37:1192-1203; MH Baumann, JS Partilla, KR Lehner, EB Thorndike, AF Hoffman, M Holy, RB Rothman, SR Goldberg, CR Lupica, HH Sitte, SD Brandt, SR Tella, NV Cozzi, and CW Schindler. Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive 'bath salts' products. *Neuropsychopharmacology* 2013, 38: 552-562; L Iversen, S Gibbons, R Treble, V Setola, XP Huang and BL Roth. Neurochemical profiles of some novel psychoactive substances. *European Journal of Pharmacology* 2013, 700:147-151.

[10] PC Meltzer, D Butler, JR Deschanps and BK Madras. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) analogs. A promising class of monoamine uptake inhibitors. *Journal of Medicinal Chemistry* 2006, 49: 1420-1432; LD Simmler, A Rickli, MC Hoener and ME Liechti. Monoamine transporter and receptor interaction profiles of a new series of designer cathinones. *Neuropharmacology* 2014, 79: 152-160; AJ Eshleman, KM Wolfrum, MG Hatfield, RA Johnson, KV Murphy and A Janowsky. Substituted methcathinones differ in transporter and receptor interactions. *Biochemical Pharmacology* 2013, 85:1803-1815.

monoamine concentrations in the central nervous system, especially in dopaminergic transmission, are thought to be involved in stimulant effects of the psychoactive phenethylamine substances.[11] Data also demonstrate that synthetic cathinones produce locomotor behavior[12] and discriminative stimulus behavioral effects[13] that are similar to those of the methamphetamine, MDMA, and methcathinone.[14] All of these studies are important tools that aid in the identification of the broad pharmacological category of a novel substance as having stimulant, depressant or hallucinogenic effects. Overall, scientific data indicate that synthetic cathinones produce pharmacology effects and stimulant-like behaviors that are similar to those of the controlled substances. Thus the goal of the drug trafficker, to make small modifications in the chemical structure of the substances while retaining the pharmacological properties of the drug to avoid prosecution, persists.

Potency of Synthetic Cathinones

There are no controlled human studies to determine the difference in potencies of synthetic cathinones. The DEA obtained data from *in vivo* animal pharmacological studies (drug discrimination studies) conducted by the National Institute on Drug Abuse on 19 cathinones. According to these studies, all cathinones fully shared discriminative stimulus effects of methamphetamine in drug discrimination studies. Animal discriminative effects are believed to parallel subjective effects in humans.[15] However, the cathinones differed in their potencies by about 40-fold from the lowest potent substance to the highest potent substance. These data also show that 17 of 19 synthetic cathinones tested showed discriminative stimulus effects of cocaine and their potencies differed by about 16-fold from the lowest potent substance to the highest potent substance. However, the order of relative pharmacological potencies of synthetic cathinones depends on the type of pharmacological assay used in determining these potencies. Because potency compares the amounts of drugs that produce the same or similar effect, users can simply adjust the dose of a given drug to achieve the desired effects. Therefore, it is not

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[11] R Rothman, M Baumann, C Dersch, D Romero, K Rice, F Carroll and J Partilla. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* 2001, 39: 32-41; T Dal Cason, R Young, R Glennon. Cathinone: An investigation of several N-alkyl and methylenedioxy-substituted analogs. *Pharmacology Biochemistry and Behavior* 1997, 58: 1109-1116.

[12] Increased locomotor activity is a common behavioral effect of stimulants. Stimulants produce a range of behavioral responses such as an increase in locomotor activity.

[13] The drug discrimination paradigm is a well-accepted animal model used to predict subjective effects of substances in humans. In the drug discrimination paradigm, if a new drug or substance has discriminative stimulus effects in animals similar to a known drug of abuse, this new drug or substance highly likely to produce pharmacological and subjective effects in humans similar to the known drug of abuse and would be similarly abused by humans.

[14] T Mori, K Yoshizawa, M Shibasaki, T Suzuki. Discriminative stimulus effects of hallucinogenic drugs: a possible relation to reinforcing and aversive effects. *Journal of Pharmacological Sciences* 2012, 120: 70-76. MB Gatch, MA Rutledge, MJ Forster. Discriminative and Locomotor effects of five synthetic cathinones in rats and mice. *Psychopharmacology (Berlin)* 2015, 232: 1197-1205; MB Gatch, SB Dolan and MJ Forster. Comparative behavioral pharmacology of three pyrrolidine-containing synthetic cathinone derivatives. *The Journal of Pharmacology and Experimental Therapeutics* 2015, 354: 103-110; MB Gatch, C Taylor and MJ Forster. Locomotor stimulant and discriminative stimulus effects of "bath salt" cathinones. *Behavioral Pharmacology* 2013, 24: 437-447; J Marusich, KR Grant, BE Blough and JL Wiley. Effects of synthetic cathinones contained in "bath salts" on motor behavior and a functional observational battery in mice. *NeuroToxicology* 2012, 33: 1305-1313.

[15] RL Balster. Drug abuse potential evaluation in animals. *British Journal of Addiction* 1991, 86:1549-158; LH Brauer, AJ Goudie, and H de Wit. Dopamine ligands and the stimulus effects of amphetamine: animal models versus human laboratory data. *Psychopharmacology (Berl)* 1997, 130(1):2-13.

advisable to use the pharmacological potency of the drug as the sole factor in determining the marijuana equivalency. Other factors such as history, patterns, scope and significance of abuse and adverse impact on the public health and social fabric also need to be considered. Evidence related to these factors suggest that synthetic cathinones are being promoted and used as substitutes for stimulant/hallucinogens such as amphetamines (e.g., methamphetamine and MDMA) and cocaine with largely similar outcomes on public health.

Cathinone Designer Drug Products

Synthetic cathinones are encountered at ports of entry. Synthetic cathinones are usually in the form of white or off-white powder, tableted, encapsulated, or supplied in small vials and bags as designer drug products.

New synthetic cathinones are rapidly introduced on the illicit market in response to domestic and international drug controls. These products containing synthetic cathinone substances often do not bear accurate labeling information regarding ingredients or the health risks and potential hazards associated with these products. This lack of information poses significant risks to users who may not know what they are purchasing or the risk associated with the abuse of those products. Analysis of three cathinone products labeled as "Eight Ballz – Ultra Premium Glass Cleaner" encountered within a few months of each other were found to have significant variance in the powder contents:

- Exhibit 1: pentylone, pentedrone, α-PBP, fluoromethamphetamine, benzocaine, caffeine
- Exhibit 2: ethylone, fluoroamphetamine, α-PVP, benzocaine, caffeine
- Exhibit 3: α-PVP, pentylone, benzocaine, caffeine

The user may be unaware of the contents and dosage and in this designer drug product example, all three products contained psychoactive substances to include multiple cathinones. Similar examples have been reported where cathinones have been identified in Ecstasy pills and capsules. With no regard for the user, these products are being distributed with no quality assurance and deceptive labeling practices. The variation of compounds encountered in designer drug products creates numerous challenges for public health and law enforcement.

User Effects

Due to the clandestine nature of use, information on user experience is limited. However, various drug user populations (e.g., clubbers, school and college students, self-reported drugs users, etc.) have been surveyed on their drug abuse patterns.[16] In general, these surveys suggest that individuals are using synthetic cathinones for their stimulant and/or hallucinogenic effects. For example, in one survey, 107 respondents compared the subjective effects of bath salts to amphetamines (65%), cocaine (58%), MDMA (53%), methamphetamine (41%), and methylphenidate (26%).[17] The desired psychoactive effects reported by abusers of synthetic cathinones include euphoria, empathy, enhanced music appreciation, hallucinations, increased insight, elevated mood, decreased hostility, improved mental function, mild sexual stimulation, a sense of well-being, increased sociability, energy, increased alertness, and improved concentration and focus.[18,19] In fact, users from drug abuse surveys reported that synthetic cathinones such as mephedrone, methylone, and MDPV have an effect profile similar to known drugs of abuse like methamphetamine, cocaine and/or MDMA.[20] For example, a web-based survey of individuals who visit websites frequented by drug users found that the effects of the synthetic cathinone mephedrone compared best with that of MDMA.[21] Participants in a survey of readers of a popular UK dance music magazine reported that mephedrone gave a better high

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[16] R Newcombe. Mephedrone The use of mephedrone (M-CAT, Meow) in Middlesbrough. *Lifeline Publications and Research* 2009, Manchester; PI Dargan, A Albert and DM Wood. Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. *QJM: An International Journal of Medicine* 2010, 103: 875-879; RL Carhart-Harris, LA King and DJ Nutt. A web-based survey on mephedrone. *Drug and Alcohol Dependence* 2011, 118: 19-22; A Winstock, L Mitcheson, J Ramsey, S Davies, M Puchnarewicz and, J Marsden. Mephedrone: use, subjective effects and health risks. *Addiction* 2011, 106: 1991-1996; AR Winstock, LR Mitcheson, P Deluca, Z Davey, O Corazza and F Schifano. Mephedrone, new kid for the chop? *Addiction* 2011, 106:154-161.

[17] PS Johnson and MW Johnson. Investigation of "Bath Salts" use patterns within an online sample of users in the United States. *Journal of Psychoactive Drugs* 2014, 46(5):369-378.

[18] L Karila and M Reynaud. GHB and synthetic cathinones: clinical effects and potential consequences. *Drug Testing and Analysis* 2010, 3: 552-559; JP Kelly. Cathinone Derivatives: A Review of their Chemistry, Pharmacology, and Toxicology. *Drug Testing Analysis* 2011, 3:439-453; JB Zawilska and J Wojcieszak. Designer cathinones – An emerging class of novel recreational drugs. *Forensic Science International* 2013, 231:42-53; JB Zawilska. Mephedrone and other cathinones. *Current Opinion in Psychiatry* 2014, 27: 256-262; CL German, AE Fleckenstein, and GR Hanson. Bath salts and synthetic cathinones: An emerging designer drug phenomenon. *Life Sciences* 2014, 97:2-8; PS Johnson, MW Johnson. Investigation of "bath salts" use patterns within an online sample of users in the United States. *Journal of Psychoactive Drugs* 2014, 46:369-378.

[19] M F Measham, K Moore, R Newcombe and Z Welch. Tweaking, bombing, dabbing and stockpiling: the emergence of mephedrone and the perversity of prohibition. *Drugs and Alcohol Today* 2010, 10:14-21; Psychonaut WebMapping Research Group. Ivory Wave report, Institute of Psychiatry 2010, King's College London: London, UK. [Paolo Deluca et al.]; EMCDDA. European Monitoring Centre for Drugs and Drug Addiction. Report of the risk assessment of mephedrone in the framework of the Council Decision on new psychoactive substances. Luxembourg: Publications Office of the European Union, 2011, doi: 10.2810/40800.

[20] RL Carhart-Harris, LA King and DJ Nutt. A web-based survey on mephedrone. *Drug and Alcohol Dependence* 2011, 118:19-22; A Winstock, L Mitcheson, J Ramsey, S Davies, M Puchnarewicz and J Marsden. Mephedrone: use, subjective effects and health risks. *Addiction* 2011, 106: 1991-1996; M F Measham, K Moore, R Newcombe and Z Welch. Tweaking, bombing, dabbing and stockpiling: the emergence of mephedrone and the perversity of prohibition. *Drugs and Alcohol Today* 2010, 10:14-2.

[21] RL Carhart-Harris, LA King and DJ Nutt. A web-based survey on mephedrone. *Drug and Alcohol Dependence* 2011, 118:19-22.

than cocaine.[22] In some instances, cathinones have become the drug of choice for experienced drug users.[23] Additional information from these studies show that users snort, swallow, and inject synthetic cathinones and the use of these substances can be associated with binge sessions that can last hours to days.[24] Users of synthetic cathinones are known to also use other psychostimulants which may lead to further toxicity.[25]

Consequences of Cathinone Abuse

Abuse of methcathinone is noted to have occurred in the U.S.S.R in the 1970's and United States in the 1990's.[26] Methcathinone was controlled by the United States in 1992 and methcathinone was placed under Schedule I of the UN Convention on Psychotropic Substances in 1994.[27] These substances are administered through insufflation, oral, smoking, rectal and intravenous methods.

Patients present to first responders and emergency departments with sympathetic stimulation and profoundly altered mental status. Altered mental status presents as severe panic attacks, agitation, paranoia, hallucinations, and violent behavior (e.g., self-mutilation, suicide attempts, and homicidal activity).[28] Bizarre behaviors are commonly connected to cathinone abuse (see below). A few noted in the literature are below:

- A 21-year-old male died from complications of *N*-ethyl-pentylone intoxication. The individual was acting erratically, so the police were called. When the police arrived, the individual was visibly upset, sweating profusely, and seemed to be paranoid. The individual began screaming, running, and trying to get into a police car when police were trying to question him. The police restrained the individual, but on the way to the hospital the individual suffered a cardiac arrest and subsequently died.[29]
- A 47-year-old man was brought to the emergency department by firemen for behavioral changes with delirious thoughts. His wife described the patient as restless and soliloquizing for the last three days. At the hospital, the patient was suspicious, anxious,

[22] A Winstock, L Mitcheson, J Ramsey, S Davies, M Puchnarewicz and J Marsden. Mephedrone: use, subjective effects and health risks. *Addiction* 2011, 106: 1991-1996; EMCDDA. European Monitoring Centre for Drugs and Drug Addiction. Report of the risk assessment of mephedrone in the framework of the Council Decision on new psychoactive substances. Luxembourg: Publications Office of the European Union, 2011, doi: 10.2810/40800.
[23] User Testimony US *v* Will, Case No. 2:13-cr-9, United States District Court, Western District of Michigan, Northern Division; K McElrath and C O'Neill. Experiences with mephedrone pre-and post-legislative controls: perceptions of safety and sources of supply. *International Journal of Drug Policy* 2011, 22(2):120-127.
[24] CL German, AE Fleckenstein, and GR Hanson. Bath salts and synthetic cathinones: an emerging designer drug phenomenon. *Life Sciences* 2014, 97(1):2-8.
[25] AM Weinstein, P Rosca, L Fattore, and ED London. Synthetic cathinone and cannabinoid designer drugs pose a major risk to public health. *Frontiers in Psychiatry* 2017, 8:156. doi: 10.3389/fpsyt.2017.00156; CL German, AE Fleckenstein and GR Hanson. Bath salts and synthetic cathinones: An emerging designer drug phenomenon. *Life Sciences* 2014, 97(1):2-8.
[26] TS Emerson and JE Cisek. Methcathione: a Russian designer amphetamine infiltrates the rural Midwest, *Annals of Emergency Medicine* 1993, 22:1897-1903.
[27] K Sikk and P Taba. Chapter Twelve- Methcathinone "Kitchen Chemistry" and Permanent Neurological Damage. International Review of Neurobology, Volume 120, 2015, 257-271;
[28] EA Ross, M Watson and B Goldberber. "Bath salts" intoxication. *New England Journal of Medicine* 2011, 967-968.
[29] Maryland Mortality Report, 2016.

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. The testing of products purchased and ingested by the subject identified MDPV.[30]

- A 41-year-old male was acting violently at his residence. The police were called. The individual was naked and agitated when the police arrived. The individual was transported to the hospital where he was pronounced dead.[31]
- A man aged between 30 and 40 years was acting aggressively and bizarre. He was driving erratically and eventually he stopped at a rest-stop where he vandalized people's property and attempted to climb a tree. After resuming travel the individual was pulled over by the police. The police noted that the man appeared mentally confused, showed no adequate reaction to the police officers requests, and violent. A toxicology screen of the individual's blood and urine samples identified α-PVP and its metabolites.[32]
- A 29-year old male was wandering outside, naked, in a state of agitation. Police described the individual as combative, flailing his arms, and disoriented. Police also stated that the individual ran out into traffic and fell onto the ground. The individual was handcuffed by the police and subsequently acting belligerently. He struggled and urinated on himself. The individual was transported to the hospital where he later died. The medical examiner concluded the cause of death was intoxication by *N*-ethylpentylone.[33]

Individuals presenting at emergency departments are often an extreme danger to themselves, other patients, and care providers and may be placed for lengthy stays in the intensive care unit to allow for the drug to be washed from their system.[34] Chronic abuse of synthetic cathinones may lead to severe neurological, cardiovascular, and gastrointestinal complications, including depression, psychosis, myocardial infarction, substance use disorder and acute liver failure.[35] Cardiovascular complications following synthetic cathinone use is very common complication attributed to synthetic cathinone use.[36] Deaths have been directly connected to synthetic cathinone consumption.[37] These dangers are well-documented and

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remain a hazard for the user who is often unaware of the substance being provided by the trafficker. Discussions of challenges for emergency services related to the cathinone class are detailed in the literature.[38]

Summary

Although there are many different cathinones, they all have structural similarities, and can be identified as cathinones. Methcathinone, mephedrone, methylone and the other cathinones detailed in Table 1 are all structurally similar and share pharmacological effects similar to cocaine, methamphetamine, and MDMA to varying degrees, which is why users seek them out. Although pharmacological potencies of synthetic cathinones vary over a range, users can simply adjust the dose for the desired effects.

In general, synthetic cathinones can be easily grouped by chemical structure. As a pharmacological drug class, synthetic cathinones share pharmacological actions with numerous controlled substances (e.g., cocaine, methamphetamine, MDEA, MDMA, etc.) to varying degrees. *In vivo* animal pharmacological studies on at least 19 synthetic cathinones show that these cathinones all have stimulant properties.

These data demonstrate synthetic cathinones pose a significant risk to the user and remain a challenge for communities. We are hopeful that the Commission adopts a class approach to cathinones, and we look forward to your questions.

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