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United States Sentencing Commission
Public Hearing: Synthetic Cathinones
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William H. Pryor Jr., Acting Chair:

Thank you for the opportunity to discuss the pharmacology of synthetic cathinones. The Commission seeks information regarding the synthetic cathinones, in particular, whether they comprise a specific class of related compounds that can be considered as a unit in terms of their pharmacology, abuse liability, and harm to the public. This information is to be used to determine whether sentencing for trafficking can be based on this unitary class or whether sentencing should be based upon marijuana equivalencies for the individual compounds.

The purpose of this statement is to address the pharmacological basis for a single class of cathinone compounds. Advantages and disadvantages of doing so are discussed in terms of the potency, intensity of maximum effects (efficacy), and adverse effects of the cathinone compounds that have been tested to date in our laboratory and others.

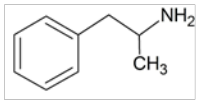
I. What are synthetic cathinones and is there a simple, clear basis for classification?

The definition of cathinone compounds is based on a common structure. The structure is quite similar to the psychostimulants in general, which are in turn quite similar in their structure to dopamine. Dopamine is well known as a neurotransmitter in brain that is very important in learning, memory, motor activity and especially reward.

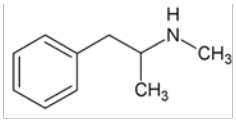
Psychostimulants were developed initially as a way to keep people awake, alert and efficient for long periods of time, and were used extensively during World War II to enhance the abilities of soldiers, pilots and others in combat. As is the way of medicinal chemistry, very many molecules are designed, synthesized and tested, to find a few compounds that are highly effective and safe. Most fail because they are not effective or are not safe. Sources for new chemicals are always being sought. Cathinone, which is found in the mildly stimulant khat plant, was used a starting point to find stimulant compounds safer and less addicting than the amphetamines.

All of the amphetamine-like compounds have the same pieces: a ring of 6 carbon atoms (phenyl-), a chain of 2 carbons (ethyl-), and a nitrogen atom (amine) at the end, that is, a phenylethylamine. The neurotransmitter dopamine shares the same basic structure. The cathinones are easily distinguished from the amphetamines by having an oxygen attached by a double bond (ketone) to the first carbon in the ethyl chain.

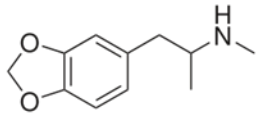
Hence, cathinone looks like amphetamine with a ketone (oxygen on a double bond) in the first carbon in the ethyl chain. Methcathinone looks like methamphetamine with the added ketone, and methylone is like MDMA with the added ketone. Not surprisingly, the cathinone compounds act very similarly to the amphetamine compounds that they resemble. Methcathinone has effects very similar to methamphetamine, whereas methylone has effects very similar to MDMA.



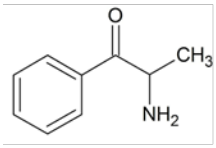
Amphetamine



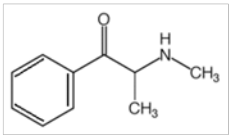
Methamphetamine



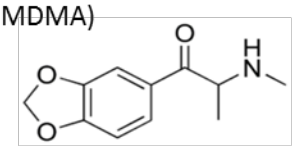
3,4-Methylenedioxymethamphetamine (MDMA)



Cathinone



Methcathinone



3,4-Methylenedioxymethcathinone (methylone)

The question posed by the Commission is whether this easily recognized structural class of compounds produces effects similar enough that they can be treated equivalently for sentencing purposes. Major factors for consideration include the range of pharmacological effects and the likelihood of harm. The following sections will consider the pharmacological efficacy (maximum intensity) of the cathinones, the range of potency of their pharmacological effects, and finally their harmful effects.

II. Common effects of the cathinone compounds

Our laboratory and others have been generating pharmacological testing for those cathinones of most concern for the Drug Enforcement Agency (DEA). The Drug Abuse Warning Network (DAWN) is comprised of emergency rooms and poison control centers around the country. When people come to emergency rooms or call poison control hotlines because of unpleasant or toxic effects after taking unknown illicit compounds, the DEA is contacted for information. For example, when people taking the first generation of synthetic cathinones reported taking "Bath Salts", the emergency room and poison control staff had no idea how to treat the acute medical emergencies induced by these "Bath Salts", so contacted the DEA to see if "Bath Salts" was a new name for known drugs or were new drugs. When the DEA does not have data on a new compound, they contract with us and other laboratories. In addition, other laboratories independently study compounds available through pharmaceutical companies.

A. Efficacy

When considering abuse liability--motivation for drug taking, it is necessary need to look at two general types of drug effects, subjective effects (also called stimulus or "cue"

effects) and reinforcing/rewarding effects. A third type of effect is the "side-effect", the off-target and adverse effects. Adverse effects will be addressed in section C.

Cathinone subjective effects. People are able to give consistent and reliable descriptions of the drugs they experience. In fact, drug aficionados ("psychonauts") report their experiences with various compounds on a number of websites, including erowid.org, bluelight.org, drugs-forum.com, etc. It is not possible to ask non-human animals about their drug experiences, but they can be trained to distinguish between the presence or absence of a drug, or between two different drugs. This "drug-discrimination" test provides a highly reliable animal model of the subjective effects of different drugs. It is very useful for a number of reasons. First, if a drug is psychoactive, animals can be trained to discriminate it. If animals cannot discriminate the drug--it is not psychoactive. Second, the drug-discrimination test predicts the likelihood of human abuse with a high degree of correlation. Third, the discrimination is based on the neurotransmitter receptor the drug works at. This allows direct testing of those receptors responsible for the subjective effects. Drug discrimination can be used across all these classes of compounds to generate marijuana equivalents; therefore, the drug discrimination test is the most reliable and universally applicable test we currently have.

Thus far, all of the cathinones tested have produced subjective effects either fully like cocaine or like methamphetamine, and most have produced subjective effects like both. Some of the compounds also produced effects like MDMA. In fact, those compounds that were not fully cocaine-like or methamphetamine-like were fully MDMA-like. Based on the subjective effects, the cathinones clearly belong to a class of related psychostimulant-like compounds, again implying that a standard based on their subjective effects (cocaine-like, methamphetamine-like, and/or MDMA-like) would likely accurately describe most of the compounds.

Cathinone reward effects. Rewarding effects can be measured by the self-administration test, in which animals are trained to give themselves drugs either orally or by an intravenous infusion. Self-administration is the "gold standard" for testing human abuse liability as it predicts quite accurately whether humans will compulsively administer a drug. Its major disadvantage is that some drug classes, (e.g. marijuana-like compounds, hallucinogens) do not produce consistent, reliable self-administration in rats. Unfortunately then, the tests of reward are not useful for making broad-based judgments about relative abuse liability across drug classes, since some drug classes cannot be tested.

Psychostimulants are known to produce their effects at dopamine receptors. In fact, how much of an increase in dopamine a compound can produce in the reward centers of the brain is directly linked to the likelihood it will be addictive. Compounds with strong dopamine receptor effects (e.g., methamphetamine) are much more likely to engender compulsive drug seeking and addiction; more serotonergic compounds like MDMA are widely taken recreationally, but seldom progress to addiction, and high serotonin compounds like the hallucinogens are taken at low rates and almost never progress to addiction.

MDMA produces its effects at both dopamine and serotonin receptors, and does not produce the same compulsive, out-of-control use as cocaine, methamphetamine and other psychostimulants. People take MDMA because it increases energy without the hard rush that psychostimulants produce and because it increases feelings of social connectedness without the sensory distortions and hallucinations that the serotonergic hallucinogens produce.

All of the cathinones tested so far are self-administered and will likely be abused by humans. The cathinones all act on dopamine and serotonin to varying degree, which can affect their reward efficacy (size of peak effect). This is measured in self-administration progressive-ratio experiments in which subjects can press a lever to get a drug administered intravenously. The cost of the drug increases geometrically over the experiment in terms of the number of lever presses. This gives a micro-economics-like measure of "elasticity"; that is, how much effort will they pay before they quit responding. Some cathinones with mostly dopamine receptor effects (pentylone or MDPV aka "Super-Coke") will support thousands of responses, whereas compounds with more serotonin receptor effects, such as butylone, will only support a few hundred.

Currently, there is data on reward strength for only a few cathinone compounds. The serotonin versus dopamine effect seems real and robust, but only a few of the most common compounds have been tested. As mentioned before, the compounds that are more serotonin-like also produce subjective effects that are strongly MDMA-like. It is possible that the cathinones can be divided into high abuse liability, psychostimulant-like compounds and low abuse liability, MDMA-like compounds. However, too few cathinones have been tested for MDMA-like effects to be able to make a strong claim.

B. Potency Range

An increasing number of cathinones are being tested, which can give us a basis for determining their range of effects and whether they can be easily categorized. The drug discrimination test is widely used for testing the potency of psychoactive effects, because it is a reliable animal model of the subjective effects of psychoactive drugs, predicts abuse liability in humans, and can be used with all drug classes.

The potencies of the cathinones tested so far mostly fall in between those of cocaine and methamphetamine, and have similar intensity of subjective effects. A single standard based on their potency would likely accurately describe most of the compounds. There have been a few cathinones that are much less potent than cocaine or methamphetamine. However, in all cases, these compounds produce reward-like effects and/or toxic effects in the dose range of cocaine, methamphetamine, and/or MDMA.

C. Adverse effects

MDMA is not very addictive; it does not drive compulsive use in most people. It is a controlled substance because it produces hyperthermia and neurotoxicity, with the result of people overdosing and dying after taking MDMA at dance clubs or "raves". Methamphetamine is also neurotoxic, and cocaine is associated with increased risk of stroke and other cardiovascular problems. Research in progress in our lab in

collaboration with neurobiology of aging researchers at UNTHSC indicates that long-term use of even low doses is neurotoxic, causing large impairments in the ability to learn and increasing vulnerability to stroke.

Therefore, the degree to which a compound is likely to produce harm is also an important issue. Some of the cathinone compounds produce extremely high blood pressure, convulsions, confusion, psychotic-like and/or aggressive behaviors. Others produce long-term harm: serious damage to brain, heart, kidney or liver, even after few doses.

Summary

The information discussed in this statement and its relevance to choosing between a single class-based or individual sentencing requirements for each cathinone can be summarized by several statements.

1. The cathinone compounds have a common and easily identifiable structural identity.
2. The cathinones all produce subjective effects similar to those of either methamphetamine and/or cocaine, and many also produce subjective effects similar to those of MDMA.
3. The cathinones have a range of rewarding effects, from those that drive highly compulsive drug-seeking to those that have only mild rewarding effects.
4. The potency of these compounds tends to be similar, lying between the potencies of methamphetamine and cocaine.
5. All of the cathinones tested so far produce some sort of harm, either high risk for addiction, short-term toxic effects, or long-term damage to heart, brain, liver or kidney.

The characteristics of easily identifiable structure, having common psychostimulant-like subjective effects with a narrow range of potencies, producing rewarding effects, and producing substantial likelihood of harm, support establishing a single marijuana equivalency for the cathinones.

Some cathinones have MDMA-like subjective effects. These MDMA-like compounds may also be much less likely to produce addiction, which is similar to MDMA. For a few other cathinones, the potencies of their subjective effects are less than those of cocaine. These data support establishing marijuana compounds for individual compounds. Currently, there is not enough data to establish whether there is a separate class of MDMA-like "entactogens" that should be treated differently than psychostimulants.