BGSU
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Acting Chair Pryor
U.S. Sentencing Commission
One Columbus Circle, NE
Suite 2-500 South Lobby
Washington, DC 20002

Dear Acting Chair Pryor,

I appreciate the opportunity to inform the panel of the strides the State of Ohio has made in writing an inclusive new approach to making classes of novel substances illegal. The language allows law enforcement to prosecute traffickers of dangerous substances faster using a method that has been used in the pharmaceutical industry for quite some time.

Please feel free to contact me if you have any questions or would like to request further information.

Sincerely,

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The State of Ohio has been at the forefront of states to experience the impact of novel psychoactive substances (NPS), in particular the synthetic cathinones. The Ohio Bureau of Investigation has been identifying these substances since 2010 and has passed various forms of legislation in order to establish the legality of possession and tracking. The various forms of legislation were all positive steps forward, but also contained flaws that needed to be overcome. The creation of the "Pharmacophore Rule" (Ohio Administrative Code 4729-11-02) is the latest and most novel approach to date.

The State of Ohio mimics the federal laws in that drugs are specifically identified by chemical or street name and placed into one of five schedules of controlled substances. While this system has worked well in the past, the ultimate flaw is that drugs can be synthetically created and are therefore not accounted for by specific name. The federal government recognized this issue and developed the Controlled Substance Act in 1986. The premise is that a novel compound that has a combination of characteristics can be considered a controlled substance even though not named in the federal register of controlled substances. In light of the current situation, the State of Ohio passed a strikingly similar act in 2011 and also named several cathinones as illegal. The major problem with instituting this analog law is that there was now the ability for defense experts to argue the language of the analog law. What may be "substantially similar in structure" to one scientist may not be substantially similar to another. Our justice allows and encourages exchange of ideas for the benefit of the accused and victim alike, but the end result is an unclear interpretation and lack of consistency.

Another attempt at more inclusive language was made on 2012. This attempt included using language enacted by other states to group compounds into classes. Ohio phrased the class in question as substituted cathinones and included language such as: "any compound…derived from 2-aminopropan-1-one by substitution at the 1-position with either phenyl, naphthyl, or thiophene ring

systems, whether or not the compound is further modified in any of the following ways" (Ohio Revised Code 3719.41). The law then further expands on what are eligible substitutions at the different positions on the molecule. While this language was the most inclusive at the time, there were still limitations that could be overcome by clever chemists that were designing compounds for illicit use.

The current "Pharmacophore Rule" is based on the theories employed by legitimate pharmaceutical companies designing compounds for legal approval. The pharmacophore of a compound is that minimum scaffold or structure that is required to bind to a drug target (e.g. receptor or enzyme) in order to elicit an effect. Receptors are targets for substances naturally produced by the body for a variety of reasons. For instance, one of the body's innate mechanisms to keep itself safe is known as the "Fight or Flight Response." In a situation of fear or excitement, the body releases neurotransmitters that increase heart rate to increase the amount of oxygen to muscles, causes vasodilation to blood vessels in muscle tissue for more energy, vasoconstriction to the stomach and intestines so more oxygen gets to muscles and a myriad of other effects. Cathinones share a scaffold with those neurotransmitters and therefore cause similar effects when ingested. By creating the Pharmacophore Rule, the State of Ohio has set a precedent for the most inclusive language in the country for classifying synthetic cathinones without the minutiae involved with classical drug scheduling.

Substantial effort has been allocated to writing a rule that is encompassing so that law enforcement can stay ahead of the criminal element. While the Pharmacophore Rule allows any chemist the ability to characterize a substance as a cathinone, there is still not enough research regarding the effects of different cathinones in the body. Of the evidence currently available, research has shown cathinones can have similarities with drugs such as cocaine, 3,4-

methylenedioxymethamphetamine (MDMA), and methamphetamine. This leads to a troubling situation where identification may be easy while determining potency becomes more difficult.

In part, studying the pharmacology of drugs of abuse is sometimes an exercise in determining similarity of effects. Does this cathinone have effects more like cocaine or more like MDMA? In a recent publication looking at several different cathinones, Gatch and others (2017) use animal models of drug-seeking behavior to demonstrate that some cathinones substitute for both methamphetamine and cocaine, but others only substitute for methamphetamine. Grecco and Sprague (2017) have shown that three structurally similar cathinones given at equal doses differ in their ability to induce a toxic hyperthermic response in a rat model. They also demonstrated that MDMA was the most potent thermogen of all the compounds tested. These diverse effects are mediated through differential binding to the neurotransmitter reuptake proteins for dopamine, norepinephrine, and serotonin.

Classical drugs of abuse all share a common pharmacological action of increasing dopamine in the synaptic terminal (Di Chiara and Imperato, 1988). Simmler et al (2012) performed an interesting study that may help separate the differences exhibited by cathinones. This study demonstrated compounds possessing a methylenedioxy bridge off the phenyl ring, like methyldioxymethcathinone (methylone), readily released serotonin by binding to the serotonin transporter. On the other hand, cathinones with no or minor substitutions off the phenyl ring readily released dopamine by binding to the dopamine transporter. But there are inconsistent compounds, such as methylenedioxypyrovalerone (MDPV), which does contain the bridge, but lacks effects on serotonin. The present showed instead, that MDPV has a profile far more similar to cocaine. Similarly, 4-methylmethcathinone (mephedrone) has a minor substitution on the phenyl ring, but succeeds in releasing serotonin and dopamine.

The Simmler study is supported by Baumann et al (2012) whose laboratory used synaptosomal release models to demonstrate methylone and mephedrone had a slightly less potent effect on dopamine, norepinephrine, and serotonin release when compared to MDMA. In the same study, the Baumann study also measured effects on movement and locomotion and noted less stimulant activity compared to methamphetamine in live mice.

A Conditioned Place Preference model in mice has shown that another cathinone, 1-phenyl-2-(1-pyrrolidinyl)-1-pentanone (α-PVP), can induce drug-seeking behavioral changes that are also exhibited by methamphetamine and morphine (Hataoka et al, 2017). Another recent study demonstrated cathinones, including methylone and α-PVP, will be self-administered in animal models, further indicating the potential for abuse (Javadi-Paydar et al, 2017).

References:

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