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William H. Pryor Jr., Acting Chair:

Thank you for the opportunity to discuss the pharmacology of synthetic cannabinoids. The Commission seeks information regarding the synthetic cannabinoids, 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, and whether these harms are different from those of marijuana (cannabis).

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 definition of cannabinoids as a class of compounds, the pharmacological effects of synthetic cannabinoids including their harms, and to compare their effects with those of marijuana and its active ingredient, Δ^9-tetrahydrocannabinol (Δ^9-THC).

I. Definition of "synthetic cannabinoids"

A. Criteria for inclusion/exclusion

Cannabinoids are defined by their ability to act directly at cannabinoid CB_1 and CB_2 receptors in the body. These actions can be measured three ways. First, cannabinoid agonists bind to cannabinoid receptors and activate them. Second, cannabinoids produce four observable effects called the Tetrad. Finally, cannabinoids produce subjective effects similar to Δ^9-tetrahydrocannabinol (Δ^9-THC, the primary psychoactive ingredient in marijuana) or to a known synthetic cannabinoid compound (e.g., JWH-018). Cannabinoid antagonists will selectively block these effects.

The Tetrad is a battery of four tests which measure: 1) decreased spontaneous locomotor activity; 2) catalepsy (loss of sensation and consciousness accompanied by rigidity of the body); 3) hypothermia (decreased body temperature) of at least 1-3° C; and 4) analgesia. All cannabinoids will produce all four effects at some dose.

Subjective effects are measured by an animal model called the drug discrimination assay. In this assay, subjects are administered a drug and given reinforcement when they make a certain response, for example, a rat pressing the left lever 10 times. On alternating days, the subject is given a placebo and given reinforcement when they make a different response (e.g., pressing the right lever 10 times). Both human and non-human animals quickly learn to make the drug-appropriate response when they receive the drug and to make the placebo-appropriate response. The drug discrimination assay both predicts with extremely high accuracy the compounds that people will say produce subjective effects like the training drug (in this case, marijuana or Δ^9-THC), and is based on the neurotransmitter receptor the drug works at (in this case, CB_1).

Unlike the cathinones, in which the class is defined by a common chemical structure very similar to the neurotransmitter dopamine, the synthetic cannabinoids come from several different structural classes: 1) Classical cannabinoids: derivatives of Δ^9-THC; 2) Nonclassical cannabinoids: synthetic derivatives of cyclohexylphenol; 3) Classical/nonclassical hybrids; 4) Aminoalkylindoles; 5) Endocannabinoids and other eicosanoids; 6) other.

All of these different structural classes have four common structural groups called "pharmacophores" that can be easily modified to produce a wide range of different compounds. It is important to note that we cannot predict whether a new compound will have cannabinoid effects by its structure. Modifying a pharmacophore in one compound could lead to several highly effective compounds, whereas modifying the same pharmacophore in another compound could produce ineffective compounds.

To conclude, whether or not a compound is defined as a cannabinoid is based on its effects, not its chemical structure. Compounds that do not produce (agonists) or block (antagonists) all the effects (receptor activation, Tetrad and drug discrimination) are not cannabinoids.

B. Cannabinoid standard

Δ^9-THC is currently the standard compound used for defining cannabinoid-like effects, because it is the primary addictive psychoactive compound in marijuana, and because the synthetic cannabinoids are primarily used as quasi-legal marijuana substitutes. The source of Δ^9-THC is

not an issue regarding its pharmacological effects. The pharmacological effects of Δ^9-THC are identical whether it is derived from the cannabis plant or is synthesized.

Marijuana is not the same as pure Δ^9-THC, since marijuana contains other bioactive alkaloids. Further, because the amounts of Δ^9-THC can vary widely between plants, the doses of marijuana and pure Δ^9-THC are very difficult to compare.

A disadvantage to the use of Δ^9-THC as the standard is that it is a low-efficacy partial agonist (see section IIB), whereas the synthetic cannabinoids are all full agonists. In addition, the synthetic cannabinoids have active metabolites that increase their duration of action, unlike Δ^9-THC. These findings suggest that there might be sufficient reason to select as a standard a compound more similar in its effects to the synthetic cannabinoids. Both WIN55,212 and JWH-018 have been trained as discriminative stimuli. However, the dose required to train WIN55,212 also produced adverse effects that interfered with the maintenance of the drug discrimination and the well-being of the subjects. In contrast, JWH-018 has been trained successfully and without difficulties in rhesus monkeys. Whether either would make a good standard for identifying synthetic cannabinoids has not been tested.

On the other hand, the subjective effects of Δ^9-THC and the synthetic cannabinoids are comparable. There are two pharmacological techniques used to assess these types of comparisons, cross-tolerance studies and antagonism studies. Tolerance is defined as the decrease in effectiveness of a drug over repeated administration. Cross-tolerance occurs when repeated administration of one drug in a class produced reduced effective of another drug in the same class—that has never been administered to the subject. For example, if a patient becomes tolerant to morphine, they will also be tolerant to another opioid, such as fentanyl or hydrocodone. Because the synthetic cannabinoids are much higher efficacy than Δ^9-THC, it is reasonable to expect that they produce a much stronger discriminative stimulus. If this is the case, then someone exposed to a synthetic cannabinoid (e.g., JWH-018) would be tolerant to Δ^9-THC; but someone exposed to Δ^9-THC would show little or no tolerance to JWH-018. However, this is not the case. Fully symmetrical cross tolerance between Δ^9-THC and synthetic cannabinoids has been reported, which indicates that the synthetic cannabinoids do not produce a stronger discriminative stimulus than Δ^9-THC.

The second technique to assess relative efficacy is the use of selective antagonists. If the synthetic cannabinoids produce a much stronger discriminative stimulus than Δ^9-THC, a larger dose of a cannabinoid receptor antagonist would be needed to block their effects than those of Δ^9-THC. Studies in our lab and others indicate that equivalent doses are necessary to block the discriminative stimulus effects of both Δ^9-THC and the synthetic cannabinoids, which again indicates that the synthetic cannabinoids do not produce a stronger discriminative stimulus than Δ^9-THC.

It is quite possible that the subjective effects and other addiction liability issues of both Δ^9-THC and the synthetic cannabinoids are functionally equivalent, and the full agonism of the synthetic compounds only contribute to their increased toxicity. This would support the use of Δ^9-THC as a standard. Further, Δ^9-THC is the primary addictive, psychoactive compound in marijuana, and synthetic cannabinoids are primarily taken as alternatives to marijuana, which suggests that in terms of social relevance, Δ^9-THC is the most appropriate standard. Finally, there is a large base of existing work in which Δ^9-THC is the standard. Taken together, these findings indicate that Δ^9-THC is likely the best standard for testing the effects of cannabinoids.

II. Pharmacological effects

A. Patterns of human use

Surveys of cannabinoid users reveal that the synthetic cannabinoids are generally marketed as safe and legal alternatives to marijuana. These compound seem to be well known, as nearly all people seeking treatment for Δ^9-THC dependence are familiar with synthetic cannabinoids. Use may be mostly limited to marijuana users as survey data suggests that people not familiar with marijuana do not like the synthetic cannabinoids. The synthetic compounds are reported to have much stronger and harsher effects than marijuana and some have more severe adverse effects. Those who choose to use them are typically seeking a different or more intense marijuana-like "high" and/or are attempting to avoid drug screens. The increased availability of "vaping" devices allow for easy administration of powdered synthetic compounds without need for injection or for converting them to a form that can be burned for smoking. Again, this is perceived as a safer alternative to smoking marijuana as the harms of smoking are avoided.

B. Data from animal models

In vitro testing. As mentioned previously, the synthetic cannabinoids bind to CB_1 cannabinoid receptors and activate them strongly. Research with the synthetic cannabinoids revealed that Δ^9-THC is a fairly weak agonist, that is, although it does bind to the cannabinoid receptors, it produces a much smaller activation of the receptor than do the synthetic cannabinoids. Most of the synthetics produce close to 100% maximal responding in tests of receptor activation, whereas Δ^9-THC produces 30-50% or less. This may be why the synthetic cannabinoids produce more severe adverse effects (described in section II C).

Tetrad. Synthetic cannabinoids produce robust effects on the Tetrad. The effects are blocked by selective CB_1 receptor antagonists, which indicates that the effects are mediated by the CB_1 receptor. Most of the Tetrad tests (except hypothermia) have ceiling effects, so they cannot measure whether the synthetic cannabinoids produce stronger effects than Δ^9-THC. At least one synthetic cannabinoid produces stronger hypothermic effects than Δ^9-THC (see section IIC).

Subjective effects. So far, all of the synthetic cannabinoids also produce subjective effects similar to those of Δ^9-THC: In mice, rats and monkeys trained to discriminate Δ^9-THC from vehicle control, all of the synthetic cannabinoids fully substitute for Δ^9-THC. The drug discrimination test also has a maximal effect, so it cannot determine whether the synthetic cannabinoids produce a stronger effect than Δ^9-THC. As with the tetrad and in vitro assays, the discriminative stimulus effects of the synthetic cannabinoids are blocked by selective CB_1 receptor antagonists, which indicates that the effects are mediated by the CB_1 receptor. Some structurally similar compounds fail to bind at CB_1 receptors. These compounds also fail to produce the tetrad and do not substitute for the discriminative stimulus effects of Δ^9-THC, and are not labeled cannabinoids.

Δ^9-THC is a fairly slow-acting compound. Subjective (discriminative stimulus) effects peak at 30 min after administration, last about 2 h, and are gone by 8 h. In contrast, some of the synthetic cannabinoids peak within 5 min and are gone within 1 to 2 h; for others, the subjective effects do not peak until 60 min after administration, and for two compounds, the subject effects took more than an hour to peak and lasted more than 24 h. Similarly, some of the compounds produced little or no suppression of responding at fully THC-like doses. Others produced deep suppression

of responding for 5 to 30 min—once responding recovers, the THC-like subjective effects are observed. Again, there is no correlation in potency or time course between the subjective and the depressant effects of cannabinoids. Whether there is a similar lack of correlation in potency between the other Tetrad tests and the discriminative stimulus effects has not been studied.

Reward and reinforcement. Place conditioning and self-administration assays have mostly failed to show consistent reinforcing effects by Δ^9-THC and/or the synthetic cannabinoids. In fact place conditioning studies have reported ranges of effects from robust aversion to mild preferences. Recent studies have suggested that the doses tested in the animal studies are relatively higher than the doses used by humans. Also, people do not tend to binge on marijuana, so the binge-like models of self-administration used for testing cocaine and other psychostimulants may not be the most appropriate. Given that humans take marijuana recreationally, it is likely that scientists just have not found the right way to model cannabinoid-taking in non-human animals.

As previously mentioned, people unfamiliar with marijuana do not like the synthetic cannabinoids. Similarly, an animal study reported that mice pre-exposed to Δ^9-THC produced a conditioned place preference to JWH-018, whereas unexposed mice produced a conditioned place aversion. Taken together, it seems that both marijuana and the synthetic cannabinoids are only rewarding in a limited set of conditions, and that marijuana use can potentiate the use of the synthetic cannabinoids.

Summary. Taken together, these findings appear to indicate a well-defined class of compounds. However, there are some difficulties in grouping all of the compounds together. First, there is poor correlation between the potencies of the synthetic cannabinoids in producing the various effects, for example, in decreasing motor activity and potency in drug discrimination. Typically, compounds in a given class produce consistent ranges of potencies across effects. For example, all opioids produce both analgesia and depress breathing, and the therapeutic window (range of safe doses) is very similar across all opioids. Second, some of the synthetic cannabinoid may produce weak or inconsistent effects. For example, one compound fully substituted for Δ^9-THC, but higher doses of the compound produced decreasing amounts of Δ^9-THC-like responding. This could indicate that while this compound may produce effects at CB_1 receptors at lower doses, at higher doses it may produce effects at other receptors. Many of the synthetic cannabinoids have only been tested for molecular effects at CB_1 receptors, so it is not known whether they produce effects at other receptors as well. Third, as previously mentioned for the drug discrimination assay, the synthetic cannabinoids produce a range of potencies and time courses, and the disparity is growing with the introduction of new compounds. The earliest of the synthetic cannabinoids to appear on the market produced discriminative stimulus effects at doses very similar to Δ^9-THC. More recent compounds are more 10-20 times more potent than Δ^9-THC, although one compound was 60-fold less potent.

C. Adverse effects

Marijuana produces a range of effects including euphoria, slurred speech, loss of fine and gross motor coordination, dizziness, dry mouth, increased appetite, and shallow breathing. Longer term use can lead to depression, loss of motivation, memory disturbance and facilitation of psychotic episodes in vulnerable individuals.

The most common adverse effects of synthetic cannabinoids are confusion, dizziness, drowsiness, agitation, irritability, nausea, vomiting, hallucinations, delusions, increased heart rate, hypertension, vertigo and chest pain. Less common central nervous system effects include headache, psychosis, seizures, myoclonus, catatonic stupor, cerebral ischemia, encephalopathy and coma. Less common cardiac effects include chest pain, myocardial infarction, and cardiac arrest. Other signs include minor elevation of blood glucose and decreased levels of potassium. Acute kidney damage and even kidney failure have been reported following use of synthetic cannabinoids.

Some of these adverse effects such as confusion, dizziness, and drowsiness are shared with marijuana, and of course, the Tetrad of depressed motor activity, hypothermia, catalepsy and analgesia are observed with all cannabinoids, whether plant-derived or synthetic. However, some of the adverse effects of the synthetic cannabinoids are more prevalent, more severe, or require less drug than in those taking marijuana. For example, hypothermia and catalepsy are typically seen only following very large doses of marijuana or Δ^9-THC and are typically mild and short-lived. One of the synthetic cannabinoids produced profound, long-lasting hypothermia (5°C) and catalepsy in rats at the dose that fully substituted for Δ^9-THC. Another example is cannabinoid hyperemesis syndrome, which is characterized by recurrent bouts of nausea and vomiting, and can occur following heavy marijuana use for years. It has also been observed following frequent administration of several of the synthetic cannabinoids, but use for several years is not necessary for the syndrome to occur. Another adverse effect common to both marijuana and the synthetic cannabinoids is psychosis. Marijuana use in adolescence increases risk of psychotic episodes, especially in individuals with genetic predisposition to schizophrenia. However, synthetic cannabinoids can produce acute and even lasting psychosis following high doses, regardless of a familial background for schizophrenia.

However, only the synthetic cannabinoids produce the most severe adverse effects, including central nervous system effects such as extreme agitation, seizures, ischemic stroke, encephalopathy and coma; cardiac effects such as chest pain, shock, myocardial infarction, and cardiac arrest; rhabdomyolysis (breakdown of muscle tissue), pulmonary complications and pneumonia; toxic effects on the kidneys and death. In vitro testing indicates that the synthetic cannabinoids are directly cytotoxic. It is of interest that many of the toxic effects appear to be caused by activation of CB_1 cannabinoid receptors, since the effects are blocked by selective antagonists. Δ^9-THC is only a weak partial agonist at CB_1 receptors, which is the most likely reason it does not cause the severe effects.

Another cause of concern is that some of the more recently seen synthetic cannabinoids are more likely to produce extremely toxic effects than the older synthetics. Waves of emergency room visits have been related to introduction of particular compounds to a geographical area, and at least one article called them "super-strength". It is not known whether the increased toxicity is due only to CB_1 effects or whether these "super-strength" cannabinoids produce effects at other receptors. One recent study has looked at other mechanisms of action in some of the older synthetic cannabinoids and reported that some produced varying amounts of activity at sites which are related to cardiotoxicity and heart disease. Whether this is also true for these newer "super-strength" cannabinoids has not been tested.

There are factors that may increase the toxicity produced by synthetic cannabinoids. First, "Spice" is often packaged as incense which contains preservatives, additives and other chemicals, as well as other active compounds such as benzodiazepines or tramadol-like

compounds, which may compound the adverse effects caused by the cannabinoids. Second, packages in powder form can also contain any number of active and inactive ingredients, which may augment the adverse effects. This was not the case when the synthetic cannabinoids were first available, as the samples were fairly pure and contained only the compound advertised on the label. Third, many of the compounds have slow onset. Users expecting a quicker high may re-dose, sometimes repeatedly, resulting in a much stronger and longer-lasting effect than expected, with an increased risk of severe adverse effects. Fourth, the synthetic cannabinoids have many active metabolites, unlike Δ^9-THC, which increase the duration of the effects, and which may interact with other receptor systems, potentially contributing to a range of adverse effects. Finally, marijuana contains several active minor compounds that ameliorate many of the adverse effects of Δ^9-THC.

It is not known how the much higher efficacy of the synthetic cannabinoids contributes to their abuse liability. Partly, this is because the role of the cannabinoid system in the normal brain is still not well understood. Partly, it is because it is not known how activation of the endogenous cannabinoid system produces either the rewarding effects or dependence. It very well may be that only low levels of cannabinoid receptor activation are necessary to produce the "high", whereas higher levels of cannabinoid receptor activation result in effects on other organ systems. If true, this would suggest that increasing the efficacy of a cannabinoid will not enhance the rewarding effects, but only add to the adverse effects. This hypothesis fits the observations that the synthetic cannabinoids do not produce stronger discriminative stimulus effects, but do produce more adverse effects.

D. Abuse liability: tolerance and dependence

Tolerance develops to the "high" produced by marijuana. Tolerance has not been extensively studied in the synthetic cannabinoids, but there is evidence in animal models than tolerance develops following repeated administration of the synthetic cannabinoids. Dependence and withdrawal is rare in marijuana users and when it does occur, the withdrawal is mild. Marijuana is not as likely to lead to dependence and addiction as other recreationally used compounds such as psychostimulants or nicotine. In contrast, dependence and withdrawal syndrome have been reported after chronic use of synthetic cannabinoids. Again, dependence and withdrawal have not been extensively studied in the synthetic cannabinoids, so the likelihood of developing dependence is not known, although the current evidence suggests that dependence is more likely with the synthetic cannabinoids than with marijuana.

It is known that drugs more likely to abused if they have a fast onset and short duration of action. Marijuana has a slow onset and consequently does not induce binging like the psychostimulants. Some of the synthetic cannabinoids have a fast onset and short action, whereas others have slow onset and very long duration of action, some more than 24 hours. Not surprisingly, those compounds with slow onset and very long duration of action are seldom seen on the street anymore since users often experience protracted adverse effects, especially if they re-dosed to hasten the onset. It is likely that the synthetic cannabinoids with rapid onset and short duration will be more likely to produce dependence than marijuana or the slow-acting synthetic cannabinoids.

III. Conclusions

Cannabinoids are a class of compounds defined by their activity at CB_1 cannabinoid receptors. Not all structurally related compounds are active, which suggests that scheduling efforts based solely upon structural features may not be useful.

The synthetic cannabinoids all produce a similar "high" to that of marijuana; however, the effects of the synthetic cannabinoids are described as much stronger and harsher than those of marijuana and some of the synthetic cannabinoids have more severe adverse effects. Some of the severe adverse effects of the synthetic cannabinoids may be mediated through other receptors (e.g., cardiac effects), but at present most of their effects appear to be mediated by cannabinoid receptors. Increasing the efficacy of a cannabinoid likely will not enhance its rewarding effects, but only add to its adverse effects.

The synthetic cannabinoids may all produce a similar "high", but the dose range is extremely wide, and there appears to be a large range in the number and severity of adverse effects produced by these compounds. There have been several publications concerned about the new "super-potent" [sic] or "super-strength" compounds which have produced waves of emergency rooms visits for severe adverse effects and traffic accidents correlated with increased use in a geographical area. Some of these new synthetic cannabinoids are related to large numbers of deaths, in contrast with marijuana for which any sort of lethality is extremely rare.

Given the wide range of potencies (300-fold), the wide range of time courses (60 min to 48 hours), the wide range of adverse effects, and the wide range of "therapeutic windows" (i.e. the range between the dose that produces the desired "high" and the dose that produces serious adverse effects), treating all of the synthetic cannabinoids as a single class may not be justifiable. Several of the newer synthetic cannabinoids appear to be much more dangerous than the early compounds. At present, it is difficult to predict whether use of a synthetic cannabinoid will lead to dependence or will have highly dangerous or lethal adverse effects. Perhaps in the future, structural differences or other features may identify distinct subclasses of synthetic cannabinoids with differing risks of harm.