UNITED STATES DISTRICT DEPARTMENT OF JUSTICE

Drug Enforcement Administration

In the Matter of **Scheduling 4-OH-DiPT, 5-MeO-AMT, 5-MeO-MiPT, 5-MeO-DET, and DiPT**	**Docket No. 22-15**

STATEMENT OF MATTHEW BAGGOTT, PH.D.

My name is Matthew Baggott. I am the CEO and co-founder of Tactogen Inc, a public benefit corporation developing novel medicines for treating mental health problems. I am a neuroscientist, data scientist, and psychedelic researcher, and have over 30 years' experience studying how psychedelics and related medicines can be made safer and more therapeutic.

I have published numerous papers going back to the early 1990s relating to the study of psychoactive substances. I have published extensively on 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), and other drugs such as alcohol, cocaine, and ketamine, evidenced by **M&TX 53** (list of publications) and **M&TX 61** (CV). I have also worked in labs that have conducted studies using methamphetamine and LSD. After graduating from the University of Chicago, I worked in a behavioral psychopharmacology lab at the University of Chicago, conducting behavioral and neurotoxicity studies with rats. I later did postgraduate work at the University of California, San Francisco, and California Pacific Medical Center, conducting human psychopharmacology studies, many of them involving drugs with measurable abuse liability. I subsequently earned a Ph.D. in neuroscience at the University of California, Berkeley and completed a postdoctoral fellowship at the University of Chicago,

conducting further human psychopharmacology studies, many of them focused on MDMA, MDA, and related compounds.

I offer this testimony as a party witness and an expert in neuroscience. I have reviewed the **M&T** references cited herein and can attest to their authenticity.

Background and Summary of Testimony

I started Tactogen to help address the mental health crisis and improve the accessibility and effectiveness of treatments for mental health. More than half of all people experience mental health challenges in their lifetime, and most do not receive adequate treatment. Some of this mental illness is severe. For these conditions, psychedelics have shown great promise. But even less severe mental health problems can potentially benefit from psychedelics and related medicines. However, because psychedelics are powerful drugs, they are typically administered in an expensive and time-consuming manner that requires many healthcare professionals. This may make treatments employing psychedelic inaccessible to many people. One reason I started Tactogen was to develop medicines that would have similar effects and effectiveness as psychedelics but that would not be as expensive and difficult to access. **M&TX 34** are printouts from Tactogen's website.

Decades ago, I began conducting research with MDMA. My research started as an undergraduate at the University of Chicago, working in the first lab to study the potential toxicity of MDMA and related drugs. My work later included assisting with the first federally funded study administering MDMA to healthy volunteers. I then led work on a comprehensive literature review of MDMA for submission to FDA by the nonprofit organization MAPS.

I personally saw how scientific and medical research on MDMA was impeded when MDMA was placed in Schedule I. I express no opinion on whether the placement of MDMA in

Schedule I in the 1980s was proper from a legal or policy perspective. Certainly there was then, unlike in the current matter of the Five Tryptamines, widely documented evidence of nonmedical use. But the deleterious consequences of that Schedule I placement are undeniable.[1] In addition to the nonmedical use of MDMA, clinicians had used the compound in psychotherapy to treat mental illnesses. Both treatment of patients and research into the effectiveness of these treatments were hindered for decades by the placement of MDMA into Schedule I. This hinderance is reflected in the slow progress of clinical research: After MDMA was permanently scheduled in 1988, it was not legally administered to humans in the U.S. again until 1994 (despite considerable efforts to initiate human research) and legal experimental MDMA therapy research in patients was not conducted in the US until 2004 (again, despite considerable efforts to initiate patient research).

Today, despite severe regulatory impediments, MDMA has been named a breakthrough therapy by FDA for treating PTSD. Nonetheless, MDMA has certain shortcomings, including short-term hypertension and long-term tolerance. One of the specific reasons I started Tactogen is to develop alternative treatments with fewer side effects that can be used in contexts where the

---

[1] Dr. Lester Grinspoon testified in those proceedings in 1985 (**M&TX 39**) and summarized the usefulness of MDMA:

> The drug of central interest here is 3,4-metbvlenedioxymethamphetamine (MDMA). When taken in doses of 75 to 150 mg orally, this phenyalkylamine seems to have a remarkable capacity to help people to get in touch with feelings, to become more open and trusting and less defensive, to facilitate the recall of early memories, and to invite self-exploration and insight. Unlike LSD and drugs with similar effects, it does not ordinarily produce perceptual distortions, body image change, or changes in the sense of self. Although MDMA is chemically related to methylenedioxvamphetamine (MDA), it is a milder and shorter-acting drug with less consciousness change and fewer secondary neurological symptoms. Adverse sequelae seem to be rare, although not unknown. In short, MDMA appears to have some of the advantages of the LSD-like drugs without most of the corresponding disadvantages.

MDMA therapy is not ideal, for example, in situations where a less powerful experience or a take-home therapy is beneficial. To do this, Tactogen is working to develop synthetic molecules that may complement or replace MDMA and classical psychedelics.

I support the appropriate scheduling of compounds when the evidence and policy considerations justify control. But I do not believe that is the case with the Five Tryptamines. Specifically, I requested a hearing in this matter for three reasons.

First and foremost, my company is developing chemical relatives of 5-MeO-MiPT as potential revolutionary treatments for mental health challenges and the proposed regulatory changes would materially affect my company. FDA named MDMA a "breakthrough therapy" in 2018 for PTSD. But many individuals with PTSD and other conditions are not ideal candidates for MDMA-assisted therapy. Based on our research, 5-MeO-MiPT and related compounds have the potential to yield medicines with therapeutic benefits that resemble those of MDMA but with fewer of undesirable effects, such as acute hypertension. These compounds may be appropriate for use with individuals who may not be candidates for MDMA-assisted therapy. Put simply, this therapy could save lives. Other than Mindstate Design Labs, I am unaware of any other company actively developing 5-MeO-MiPT. And if DEA places 5-MeO-MiPT into Schedule I, Tactogen will likely need to abandon its development efforts to produce analogues of 5-MeO-MiPT.

This abandonment will be necessary because regulation of chemicals using the Controlled Substance Act is not compatible with how modern, early-stage drug development companies work with chemicals. Today, such companies rely on commercial vendors to perform different specialized tests. Studying a Schedule I controlled substance would require each vendor obtain a license for the substance. This process would be slow and expensive, and many vendors would be unwilling to take on the additional burdens. In comparison to companies in Canada and

other countries that have not made the Five Tryptamines into explicitly controlled substances, Tactogen and other U.S. companies would be at a severe disadvantage in terms of working in this area. Research to develop derivatives of 5-MeO-MiPT would also be slowed by the fact that the placement of 5-MeO-MiPT into Schedule I of the CSA automatically also schedules a large number of other related molecules called positional isomers. Even though many of these positional isomers are completely unstudied, they would each require Schedule I permits before they could be synthesized and studied.

In general, I believe that the regulations of chemicals should be adequate to keep individuals safe and protect public health. But these regulations should also not unnecessarily harm businesses and decrease the competitiveness of U.S. businesses in comparison to ones in other countries. The current proposal to schedule the Five Tryptamines fails to balance these considerations.

Second, I believe the science presented by DEA and HHS in this matter is flawed. The drug discrimination testing, which is used to claim similarity between the Five Tryptamines and various Schedule I and II controlled substances, lacks scientific rigor. The testing is biased in a way that makes it likely conclude that the Five Tryptamines are similar to the Schedule I and II substances, whether or not this similarity exists in reality. Most glaringly, no formal statistical evaluation is used to distinguish chance findings from real patterns. Human evidence of similarity between the Five Tryptamines and the Schedule I substances is also lacking. For example, as typically used by people, 5-MeO-MiPT does not have effects that are substantially similar to DMT or LSD or DOM. Evidence suggests 5-MeO-MiPT has greatly enhanced emotional and interpersonal effects and reduced propensity to create visual distortions compared to these common psychedelics.

Third, I have seen no evidence to suggest the five tryptamines have a "high potential abuse" let alone any significant potential for abuse. Clearly, over the past two decades, there have been instances of isolated or occasional use. Many unscheduled substances are occasionally abused. But I see no evidence showing levels of abuse of 5-MeO-MiPT that would warrant control in Schedule I or anything beyond the restrictions already imposed by the Analogue Act, which already regulates human use of the Five Tryptamines.

Neurochemistry Fundamentals

The exhibits in this case discuss certain neuroscience concepts, which I briefly summarize below, defining and explaining a few terms in my testimony and in the documents.

Scientists use different types of tests to characterize drugs. Studies that employ animals are called ***in vivo*** studies, while studies that employ cells growing in containers are called ***in vitro*** studies.

Monoamine neurotransmitters are neurotransmitters that regulate mental processes. Thus, the systems of neurons that use monoamine neurotransmitters play important roles in cognition and mental illnesses. It is thought that dysregulation in these systems can contribute to neurological or psychiatric disorders such as depression, anxiety, and PTSD. Drugs that aim to treat these disorders often do so by regulating or modulating neurotransmitter systems.

There are three major monoamine neurotransmitters: serotonin, dopamine, and norepinephrine.

Serotonin (5-HT) is a neurotransmitter, monoamine, and neuromodulator signal throughout much of the brain, adjusting the stability of ongoing brain processes in response to changing environmental influences, and affects sensory and other neurons. The biological function of serotonin is complex. Serotonin regulates mood, appetite, learning, memory, and

numerous physiological processes in the body (Nichols & Nichols 2008 **GX15** at 455-56). Serotonin also often mediates the hallucinogenic effects of drugs. Our early understanding of serotonin came in large part through the discovery and science of LSD, marking the beginning of the era of modern neuropsychopharmacology (Nichols & Nichols 2008 **GX15** at 457).

Dopamine (DA) is a monoamine neurotransmitter that plays an important role in executive functions, motor control, motivation, attention, memory, arousal, sexual gratification, reinforcement, and reward. Most drugs of addiction involve the modulation of dopamine in some manner, whether by increasing dopamine release or blocking the reuptake of dopamine following release.

Norepinephrine (NE) is a monoamine neurotransmitter that plays an important role in arousal and alertness, vigilance, memory, and focus/attention.

A **receptor** is a protein that resides on the surface of a brain cell. Chemical neurotransmission—or the process of brain cells communicating with one another—happens when one brain cell releases a neurochemical into the liquid-filled space in between neurons. For a neighboring cell to receive the message, that neurochemical must bind with one of its receptors. A lock/key metaphor is often used to describe neurotransmission. When a key (neurotransmitter) fits into a lock (receptor), the receptor is activated and activity inside the cell is altered.

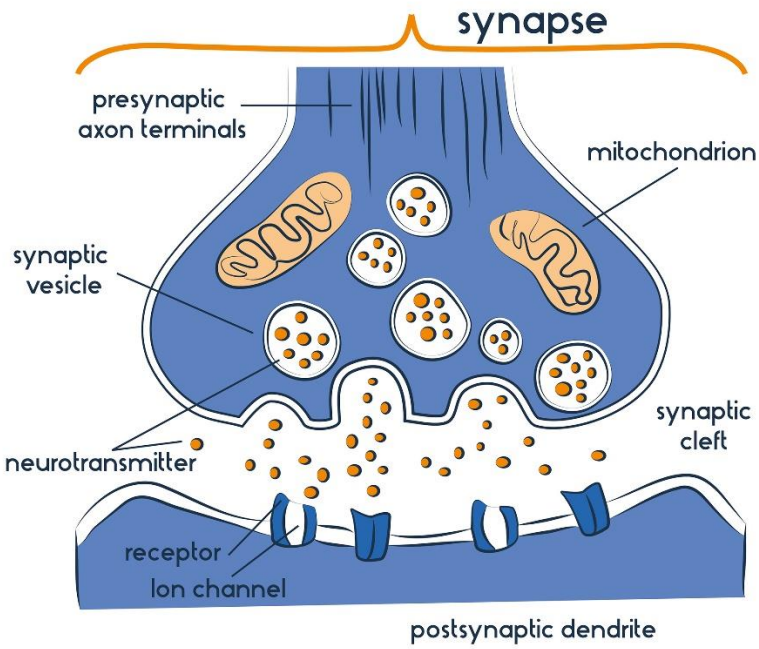
Serotonin receptors (or 5-HT receptors) (the locks) alter activity with their neuron, often affecting the release of other neurotransmitters such as dopamine, glutamate, or GABA. There are seven known families of serotonin receptors, 5-HT1 through 5HT7 (Nichols & Bush 2001 **GX15** at 448). Within each family, there are subtypes. For example, the 5-HT1 family has five subtypes: 5-HT1A, 5-HT1B, 5-HT1D, 5-TH1E, 5-HT1F (Nichols & Nichols 2007 **GX15** at 471-

74). Needless to say, these receptor subtypes are not all the same. As Nichols & Nichols explain, they have different shapes, are made of different sequences of amino acids, and perform different functions when activated.

These serotonin receptors (locks) are activated by the neurotransmitter serotonin (key). 5-HT receptors can mediate both excitatory and inhibitory neurotransmission. The different families of serotonin receptors and subtypes do not perform the same function when activated. Our knowledge of the serotonin system is still developing, and only recently have we made meaningful progress in understanding how it works (Fantegrossi 2008 **GX15** at 537, 541).

Monoamine **transporters** move monoamines into cells. There are three main types of monoamine transporters: the dopamine transporter (DAT), the serotonin transporter (SERT), and the norepinephrine transporter (NET). Each of these transporters moves the specific monoamine from the synaptic cleft of a cell to the presynaptic neuron. In other words, monoamine transporters are the shuttles that move keys into storage.

The image below from Simple Psychology shows a **synapse**. The synapse is the small gap between two neurons, where nerve impulses are relayed by a neurotransmitter from the presynaptic (sending) neuron to a postsynaptic (receiving) neuron:



As discussed above, drugs that aim to treat mental or neurological conditions frequently target and modulate monoamine neurotransmitter systems. These drugs can modulate these systems in several ways.

For example, monoamine oxidase inhibitors (**MAOIs**) are a class of antidepressants that inhibits the enzyme monoamine oxidase. Monoamine oxidase breaks down monoamines released by neurons, including, serotonin, dopamine, and norepinephrine. MAOIs include drugs like selegiline and harmaline. Thus, MAOIs change the levels of neurotransmitters by preventing the breakdown of the monoamine neurotransmitters in the brain. MAOIs have been used to treat depression. In general, MAOIs are safe to use, but can be dangerous, possibly fatal, when combined with other drugs that affect neurotransmitter systems.

Reuptake inhibitors are another type of medication used to treat neurological or psychiatric disorders. Reuptake inhibitors, which include SSRIs (selective serotonin reuptake inhibitors), SNRIs (serotonin and norepinephrine reuptake inhibitor), and others, inhibit the

monoamine transporters that normally recapture released neurotransmitters. It is hypothesized that by inhibiting neurotransmitter reuptake, more neurotransmitters are present in the extracellular fluid and are available for binding to receptors.

Some drugs increase levels of neurotransmitters by releasing monoamines. A common example of a releasing agent is amphetamine, which is used in the treatment of ADHD (Attention Deficit Hyperactivity Disorder). Amphetamine acts to release dopamine and norepinephrine by altering the functioning of their respective transporters, causing them to work in reverse.

Other drugs work by activating or preventing activation of receptors. **Agonists** are substances that bind to specific receptors and cause activation of processes inside the cell, thus mimicking the effect of an endogenous neurotransmitter. A 5-HT1A agonist, for example, is a serotonin agonist that binds and activates 5-HT1A receptors. The compound buspirone acts as 5-HT1A receptor agonist and is thought to treat anxiety without the side-effects and dependence potential of benzodiazepines (Nichols & Nichols 2008 **GX15** at 471-72). Drugs that target or modulate 5-HT1A receptors may be useful in treating depression (Nichols & Nichols 2008 **GX15** at 471-72)[2].

A **partial agonist** is a drug that binds to a receptor and activates processes in a cell, but only has partial ability (called efficacy) to stimulate activity inside the cell compared to a full agonist or the neurotransmitter that normally stimulates the receptor.

In contrast, an **antagonist** will bind to synaptic receptors but decrease a specific activity in the cell compared to activity that occurs when the neurotransmitter binds to the same receptor. A 5-HT1A antagonist, for example, is a drug that binds 5-HT1A receptors and decreases specific

[2] The drug vilazodone is an example of an antidepressant with partial agonism on 5-HT1A receptors.

activity with the cell. For example, schizophrenia is thought to involve irregular dopamine activity, so most antipsychotic drugs are dopamine antagonists, which reduce activity in cells containing specific dopamine receptors.

The binding strength of an agonist or antagonist can be measured with radioligand assays. These assays are the gold standard for measuring the affinity of ligand binding to a target receptor, due to their robustness and sensitivity. The binding strength is measured with the inhibitory constant **Ki.** The *smaller* the Ki, the greater the binding affinity.

In contrast, the ability of an agonist or antagonist to alter activity in the cell that bears receptors is measured with assays that typically yield measures of potency (the concentration needed to produce a change) and efficacy (the amount of change produced).

The Role of Serotonin Receptors in Hallucinogens

Current science does not allow us to examine data on the interactions of a drug with receptors and reliably infer whether that drug will have hallucinogenic effects, such as those produced by LSD, DMT, and DOM. To produce such hallucinogenic effects, it appears necessary for drugs to bind to and stimulate the 5-HT2A receptor. However, this is not sufficient: some drugs that bind and stimulate 5-HT2A lack hallucinogenic effects. It is possible that this difference in hallucinogenic potential may be caused by subtle differences in how the drugs stimulate the receptor. It is also possible that stimulation of other receptors modifies the hallucinogenic potential of drugs that stimulate 5-HT2A. I discuss these matters in more detail in this section.

Several lines of evidence indicate that stimulation (that is, agonism) of the 5-HT2A receptor is most responsible for hallucinogenic effects (**M&TX 5** at 2; Nichols & Nichols 2008 **GX15** at 467; Nichols 2016 at 338). Indeed, classical psychedelics, such as LSD and psilocybin,

are 5-HT2A agonists. Other drugs that are not considered classical psychedelics, but which produce hallucinogen-like effects, are 5-HT2A agonists as well. For example, the drug lorcaserin (Schedule IV) is a 5-HT2A agonist and is capable of producing hallucination-like effects at high doses (**M&TX 7** at 4, 8, 12; **M&TX 36** at 3, 5**)**. The antimalarial drug mefloquine (unscheduled) is a partial 5-HT2A agonist and capable of causing visual hallucinations (**M&TX 11**). Some hallucinogenic drugs bind exclusively to 5-HT2A (Nichols & Bush 2001 **GX15** at 448). Others bind to a variety of receptors in addition to 5-HT2A.

While stimulation of the 5-HT2A receptor is likely necessary for the effects of the classic psychedelics such as LSD, psilocin, and mescaline, it is likely not sufficient (Nichols 2016.). Some compounds show ability to stimulate the 5-HT2A receptor but apparently do not have hallucinogenic effects at typical doses. Lisuride is an example of a compound that binds to and stimulates 5-HT2A receptors with high potency but which lacks hallucinogen-like effects (**M&TX 6** at 13, discussing lisuride; Fantegrossi 2008 **GX15** at 546). Based on this and other examples, it appears that interactions of a drug with other binding sites are able to modify and/or mediate effects of 5-HT2A agonists **(M&TX 6)**.

Overall, the relationship between the 5-HT2A receptor and hallucinogenic effects is not straightforward. In particular, (1) the ability to bind to 5-HT2A does not imply the ability to stimulate or produce specific effects of interest and (2) effects at other receptors can significantly modify effects of a 5-HT2A agonist. As a result, to understand the effects of a hallucinogenic compound fully and reliably, one cannot look at the 5-HT2A receptor alone. It is important to look at effects on many other receptor sites, such as 5-HT1A, 5-HT1B, and 5-HT2C that can contribute to perceptual, cognitive, emotional, and other neural processes.

I agree with the following from Nichols (2016 **GX15** at 419):

> Even with the development of modern brain scanning technologies, however, the overall action of psychedelics in the brain is far from being understood. Psychedelics act as agonists or partial agonists at serotonin 5-HT2A, 5-HT2C, and 5-HT1A receptors, with downstream effects on glutamate, GABA, and dopamine, among others, in a multitude of loci in the brain (Vollenweider and Geyer, 2001). Although it is the scientific consensus that activation of brain 5-HT2A receptors is the central event in the action of psychedelics (Nichols, 2004; Halberstadt, 2015), that statement of what outwardly might seem to be a simple pharmacology fails to completely capture the overall consequences of that action within the dynamic interacting human brain.
>
> Brain imaging studies have begun to offer some preliminary answers. But a tremendous amount of science remains to carried out before (or if) we can begin we can begin to understand the complex psychopharmacology that occurs in the intact human brain after administration of a psychedelic such as LSD.

Fantegrossi (2008 **GX15** at 546) notes that hallucinogenic and non-hallucinogenic 5-HT2A agonists both activate 5-HT2A but activate a different set of genes. Fantegrossi concludes, "that hallucinogenic compounds display widely divergent affinities for the 5-HT2A receptor, that some putative non-hallucinogens display high affinity for the receptor, that some hallucinogens display a lack of affinity for the receptor, and that a correlation can be drawn between hallucinogenic potency in man and affinity for serotonin receptor subtypes not known to have a role in hallucinogenesis, it seems plausible to speculate that the 5-TH2A receptor may not be the sole mediator of hallucinogenic effects" (Fantegrossi 2008 **GX15** at 547).

Indeed, research supports the conclusion that other receptors are involved in mediating hallucinogenic effects. For example, Nichols (2004) describes how other serotonin receptors contribute to the hallucinogenic effects (**GX15** at 151-53). He discusses how it is possible that activation of the 5-HT2C receptor may play a role in the overall intoxication process in man. Also, Nichols suggests that the 5-HT1A receptor also may place a significant role in the quality and strength of effects. Fantegrossi (2008) posits that the 5-HT1A receptor can play a modulatory role in hallucinogenic effects, as well as many other receptors (**GX15** at 547-48,

discussing role of 5-HT1A receptors, 543 discussing role of dopamine receptors). I further note that Fantegrossi concludes, in 2008, that then "[c]urrent methods in behavior pharmacology and neuroscience are finally beginning to chip away at the mystical façade that has defined the hallucinogens for too long" (**GX15** at 550).

In sum, the neurochemical and hallucinogenic properties of psychedelics cannot be assessed by looking at 5-HT2A alone. Nor would it be sufficient to look only at 5-HT2A and 5-HT1A to determine the hallucinogenic properties or to compared one or more drugs. Hallucinogens and drugs that act on that 5-HT2A vary considerably. While many produce profound dramatic visual alterations, others do not, possibly due to activity on other receptors and/or effects on other aspects of the monoamine system, such as transporters and reuptake inhibition. The implication of this is that in vitro studies alone cannot provide reliable evidence of whether and to what extent a drug is hallucinogenic.

Animal Drug Discrimination Studies

The evaluation of the abuse liability of the Five Tryptamines relies to a great extent on data from rodent drug discrimination tests. These tests can provide useful information, but the way that they are being conducted and interpreted here creates severe biases to categorize the Five Tryptamines as similar to well-known Schedule I and II substances with abuse liability. Accordingly, I believe the drug discrimination test results are not currently interpretable and should not be relied on for regulatory decision making.

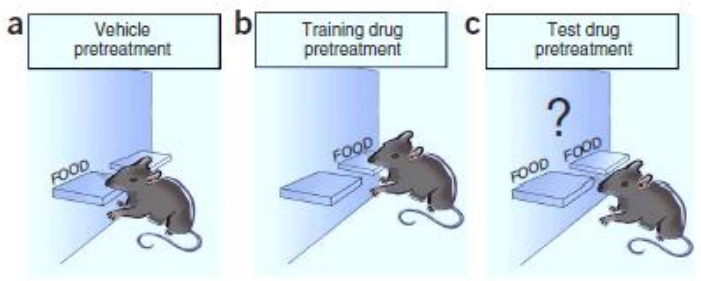
A first way that this evaluation is biased is that the Five Tryptamines are only compared to Schedule I and II controlled substances rather than to both controlled substances and drugs that affect brain functioning but lack abuse liability, such as antidepressants or antipsychotics. This is analogous to asking how similar milk is to different types of alcoholic beverage. One will

invariably conclude that milk is at least a little similar to alcoholic beverages and this might even suggest to some that society should reconsider our regulation of milk. Yet this apparent similarity does not mean that milk is not also similar to nonalcoholic beverages such as fruit juices. In fact, milk is arguably more similar to fruit juices in that both provide nutrition and neither causes inebriation. Comparing milk only to alcoholic beverages only provides evidence in one direction and leads to an interpretive bias. The same type of selective comparison creates bias in the case of the Five Tryptamines.

A second way that this evaluation is biased is because the researchers conducting the tests do not use statistical procedures to distinguish animal responses that happen randomly from animal responses that truly show the Five Tryptamines are similar to the training drugs (which, again, are all well-known Schedule I and II controlled substances). The use of multiple controlled substances also creates a high probability that each of the Five Tryptamines will be found to be similar to one or more controlled substances by chance simply because there are so many opportunities for chance findings. Similarly, in these experiments, the test drug dose is escalated and additional trials are conducted until the animals are too impaired to respond and stop responding or until the dose is very high. The multiple dose levels function as multiple "shots on goal" and increase the probability of erroneously finding by chance that the test and training drugs are similar even if they are not similar in reality.

To explain the risk of chance findings, it is necessary to describe the drug discrimination procedure in some detail. In a two-lever drug discrimination test, each animal is trained to produce one response (here, a lever press) during experimental sessions shortly after the administration of a particular drug (the "training drug") and produce a different response (pressing a different lever) during sessions that follow administration of a drug-free placebo.

Accordingly, animals learn to associate one lever with the training drug and another with the placebo. During training, the animals are rewarded with food when they complete some number of correct lever presses (here, ten presses). Once the animals reliably perform this task, a novel drug can be tested for similarity to the training drug. During test sessions that follow administration of a novel test drug, animals are rewarded with food after some number of lever presses, regardless of which lever they press. The general two-lever protocol, is illustrated below in Solinas (2006 **GX15** at 615).



Presses on the drug associated lever are counted as evidence that the test drug is similar to the training drug. This is most often quantified and expressed as the percent of training-drug-appropriate lever responses. When the percent of training-drug-appropriate lever responses is 20% or above but less than 80%, there is a convention among researchers to say that the test drug is "partially substituting" for the training drug and that responses are "partially generalizing." Similarly, when the percent of training-drug-appropriate lever responses is 80% or greater, then the test drug is conventionally said to "fully substitute" for the training drug and responses are said to "fully (or completely) generalize". Partial and full substitution are seen as two levels of evidence of similarity between the test and training drug.

The interpretation of partial substitution or generalization is an ongoing subject of debate—especially with complex drugs (Solinas 2006 **GX15** at 624). It is important to note that,

from a statistical point of view, partial substitution is what we would expect to see by chance. After all, there are only two levers, so animals have a 50% chance of selecting the drug-associated lever at the beginning of a test session. And, as pressing this lever results in food rewards, most animals will continue to press the first lever selected in the test session, even if the initial selection of this lever was random. Because of this, what is called partial generalization or partial substitution –which is the majority of drug discrimination data produced by the Five Tryptamines– cannot, without careful statistical evaluation, be distinguished from how animals would respond if they were responding randomly or if they received a drug that had no abuse liability and was not similar to any of the training drugs.

This issue is particularly salient in the case of 5-MeO-AMT, which did not fully substitute for any training drug and is interpreted to have partially substituted for LSD. When individual animal data are examined, it is clear that this alleged similarity to LSD is based on only two of the six animals consistently selecting the LSD-appropriate lever after a single dose level. This is simply not credible evidence that 5-MeO-AMT has LSD-like effects.

Compared to partial substitution, or full substitution (also called full generalization), can be considered somewhat stronger evidence that the test drug and training drug are similar. However, because animals tend to use a consistent lever in each session and there are six animals in each testing cohort, full substitution here can simply mean that four or more of the six animals have selected the training-drug-appropriate lever. When animals use consistent levers, the probability of full substitution occurring by chance (i.e., because the animals have randomly selected a lever) is the same as the probability of flipping six coins and having at least four land heads up, or 34.375%. When a novel test drug is compared to six training drugs, as is the case here, and each has a 34.375% probability of full substitution, then the chance of seeing at least

one full substitution is 1-((1 - 0.34375)^6) or approximately 92%! In other words, if the test drug had no abuse liability and did not have effects resembling the training drugs, the evaluation process would still incorrectly conclude the test drug substituted for one or more training drugs in over nine out of ten times.

In addition, the researchers use a dose escalation process where they test increasingly higher doses until either the majority of the animals stop responding or the dose reaches 100 mg drug per kg body weight. Each dose level provides another opportunity for full substitution (i.e., 4 or more animals consistently selecting the drug-associated levers) to occur by chance. When full substitution occurs, whether or not it is by chance, the researchers do not conduct further trials with higher doses or otherwise verify the apparent substitution. Given these procedures and the failure to account for chance events, it is probable that any drug tested would appear to have abuse liability!

In the case of drug discrimination testing of 5-MeO-MiPT, the researchers reported that 5-MeO-MiPT only fully substituted for DOM and did not fully substitute for other training drugs. However, the DOM data appear exactly as would be expected from a chance finding: several earlier doses provided equivocal findings with inconsistent animal behavior before one dose provided the behavior that the researchers were looking for. Injected doses of 0.25, 0.5, and 1 mg 5-MeO-MiPT per kilogram body weight produce results that are consistent with animals randomly selecting a lever. This can be seen in the low consistency of lever selection by the individual animals. For example, of the three animals that primarily select the drug-associated lever after receiving 0.25 mg drug per kilogram body weight, only one animal also primarily selects the training-drug-associated lever after receiving the next higher dose. The same lack of consistency is also seen when animal responses are compared between the 0.5 and 1.0 dose

levels. Therefore, when all animals select the training-drug-associated-lever after the highest dose of 2.5 mg 5-MeO-MiPT per kg body weight, there is no evidence from lower doses that animals were becoming gradually more likely to select the training-drug-appropriate lever as doses are increasing. Instead, it appears possible that the animals have, only by chance, primarily selected the training-drug-appropriate lever and that this chance event (which has a probability of approximately 34.375%) has led the researchers to stop escalating the dose and stop collecting data.

The same observations can be made about the claims that 4-OH-DiPT fully substitutes for DOM and LSD, that 5-MeO-DET fully substitutes for DMT, and that DiPT fully substitutes for DOM and DMT. In the case of 5-MeO-DET allegedly fully substituting for DMT, it is noteworthy that only three of the six animals appear unimpaired and are consistently responding. Thus, although most responses employ the training-drug-appropriate lever, half of the animals are not performing the task, which increases the probability that the remaining animals will select the same lever by chance. After all, the probability of three coins landing heads up is higher than the probability of six coins landing heads up. In all these claims about full substitution, it is possible that the animal behavior is driven by chance rather than the by actual similarities of the test and training drug.

Neither the researchers conducting the drug discrimination testing nor HHS nor DEA use formal statistical evaluation to distinguish real patterns of substitution from ones produced by chance. It is very unusual in science for evaluation of a procedure to omit formal statistical evaluation. And it is striking that the researchers performing the drug discrimination testing use formal statistical evaluation of animal response rate but omit formal statistics for interpreting of choice of lever. The lack of formal statistical testing creates a bias to see abuse liability where it

may not exist. This bias could be corrected by using formal statistical testing and the testing procedure could be further improved by including training drugs that lack abuse liability. Alternatively, full substitution could be confirmed by collecting additional data at the same or a similar dose as the one that showed full substitutions. Without such correction, I believe the results of the drug discrimination tests cannot be reliably interpreted.

As a final comment on the drug discrimination testing, it should strike us as odd that this drug comparison procedure is being interpreted as providing evidence of abuse liability. Rat drug discrimination studies are "only an indirect measure of the abuse potential of a drug" (Solinas 2006 **GX15** at 615). After all, when the animals indicate that two drugs are similar, they do not indicate that the similarities include qualities relating to abuse, such as euphoria, drug liking, or drug craving. In fact, it is possible that animals are instead perceiving similarities in somatic sensations, such as headaches or feeling warm or cold, that are unrelated to abuse liability. The drug discrimination process simply does not allow us to infer the basis on which animals are comparing the test and training drug. This is why, in the context of developing new prescription medicines, drug discrimination findings are not seen as strong evidence of abuse liability. Instead, they are taken as an indication that further evaluation, ideally in humans, is warranted. Ultimately, drugs that appear similar based on drug discrimination data cannot be expected to share abuse liability.

Drug discrimination testing is also particularly difficult to interpret in the context of psychedelics. Nichols (2004 **GX15** at 153) explains that "caution must still be exercised in extrapolating rat drug discrimination data to humans" and that rat and human 5-HT2A receptor subtypes have somewhat different structure-activity relationships, so effects of various psychedelics on rat behavior, including behaviors relating to abuse liability, may not strictly

parallel those in humans. Similarly, Heal (2018 **M&TX 23** at 10) explains that psychedelics and other drugs affecting serotonin receptors yield results that do not make sense based on human experience or basic pharmacology:

> Nothing is ever that simple and it has been reported that the 5-HT antagonists, methysergide and mianserin, generalise to LSD (Colpaert et al., 1982) and the 5-HT1A agonist, 8-OH-DPAT (2-(di-npropylamino)-tetralin), generalised partially to LSD (Benneyworth et al., 2005; Reissig et al., 2005). Furthermore, MDMA does not generalise to LSD (Appel et al., 1982; Callahan and Appel, 1988; Baker and Taylor, 1997) even though its discriminative cue has a 5-HT2A receptor agonist component (Fig. 1; Baker et al., 1997; Goodwin et al., 2003). In other drug-discrimination experiments, LSD and psilocin, but not mescaline, were observed to generalise to the psilocybin (Koerner and Appel, 1982), and while MDMA generalised to the cue elicited by mescaline, it generalised to saline in LSD trained rats. in LSD trained rats (Callahan and Appel, 1988). These psychedelics are not highly selective 5-HT2A agonists and a failure to observe cross-generalisation could be due to that fact. However, similar discrepancies have been reported for more selective compounds where for example 25CN-NBOH only partially generalised to the discriminative cue elicited by DOI (Fantegrossi et al., 2015). In another case, the selective 5-HT1A agonists, 8-hydroxy-2-dipropylaminotetralin (8OH-DPAT) and buspirone, and the antagonist, ipsapirone, generalised to the cue elicited by 5-MeO-DMT (Spencer et al., 1987). **For these reasons, we are of the view that 5-HT2A agonists are not the ideal choice as training drugs in drug discrimination experiments where the objective is to identify whether novel drug-candidates have (i) psychedelic properties and/or (ii) pose a risk of abuse.**

This last point bears emphasis because DOM, one of the training drugs used in the drug discrimination studies relied upon to assess abuse liability of the Five Tryptamines, is a selective 5-HT2A agonist.

Ultimately, reliance on drug discrimination tests to assess abuse liability can be questioned when there are several behavioral animal tests that more directly measure abuse liability, including drug self-administration tests and conditioned place preference tests. One possible reason that these more direct tests are not being employed is that psychedelics show low abuse liability in these tests. To the extent that the Five Tryptamines are psychedelics, it is, in my

opinion, likely that these more direct tests would fail to find evidence that the Five Tryptamines have significant abuse liability.

Human Evidence for Abuse Potential of the Five Tryptamines

I have previously discussed how in vitro studies of drugs interacting with receptors do not provide reliable evidence that the drugs will be hallucinogenic. I have also discussed how biases in design and the lack of formal statistical testing prevents reliable interpretation of the drug discrimination tests and how these tests only provide very limited evidence of abuse liability. Now, I discuss human evidence that the Five Tryptamines have high potential for abuse. One indication used by DEA is whether any of the Five Tryptamines are being taken in amounts sufficient to create a hazard to their health. As a general matter and with few exceptions, hallucinogens are typically regarded as physiologically safe molecules that have low toxicity (Nichols 2004 **GX15** at 146). Consistent with this, there is a lack of reports of overdose or other toxicity from people using the Five Tryptamines. Instead, DEA describes rare case reports of polydrug use.

Cases involve polydrug use should not be considered evidence that the Five Tryptamines are being used in amounts that are a hazard to health. This is because increased toxicity from polydrug administration is a known phenomenon for very many drugs that DEA and medical experts do not regard as inherently hazardous to health.

For example, DEA's Eight Factor Analysis reports that one death associated with 5-MeO-AMT, but notes that it is "unclear what role 5-MeO-AMT played in the death" (**GX 11** at

19). It similarly notes that a non-lethal poisoning was reported in 2005 of an adolescent after allegedly combining 5-MeO-MiPT and harmaline (**GX 11** at 19).[3]

These instances of polydrug use—combining two or more drugs together—do not reflect the dangers of these substances or potential for abuse. Many drugs, which may not be dangerous or lethal on their own, become dangerous or significantly more dangerous in combination with other drugs. Mixing alcohol with a common ingredient with cough medication, for example, can be fatal in sufficient doses.

In the cases of the polydrug reports in the Eight Factor Analysis, it is well-known that otherwise safe serotonergic drugs often do not mix MAOI inhibitors (such as harmaline) and other antidepressants. As such, these reports do not appear to reflect the danger of either 5-MeO-AMT or 5-MeO-MiPT in isolation. Moreover, I have seen no evidence to suggest that these drugs are frequently used with antidepressants.

To summarize this section, cases of drug interactions leading to adverse events are very common and are not generally taken as evidence that the individual drugs are hazardous. Such cases also cannot be taken as evidence that the individual drugs have abuse liability.

Lorcaserin

I have discussed how the process for evaluating the Five Tryptamines is biased and unreliable. This can be contrasted with how the weight loss drug lorcaserin was evaluated by HHS and DEA. Lorcaserin also causes hallucinations in supra-therapeutic doses and can

[3] The HHS report refers to an additional case involving a 25-year-old man found dead after consuming a "cocktail" including 5-MeO-MiPT (**GX 9** at 5, 8). This too is a polydrug use case.

stimulate 5-HT2A. In evaluating lorcaserin, DEA expressly rejected notions that being a 5-HT2A agonist is sufficient to show a high potential for abuse.[4]

Lorcaserin is a 5-HT2A agonist and has hallucinogen-like effects (**M&TX 7)**. DEA noted in 2012 that a drug discrimination study in rats showed lorcaserin produced responses similar to the Schedule I hallucinogen DOM (**M&TX 7** at 6, **M&TX 36** at 5). While HHS claimed that the pharmacology of lorcaserin most closely parallels LSD and psilocybin, when HHS reviewed the human abuse potential, they compared lorcaserin to the Schedule III drug ketamine (an NMDA antagonist) and the Schedule IV drug zolpidem (a GABA agonist, brand name Ambien). The result of that comparison showed that lorcaserin, at higher than recommended doses, produced euphoric, hallucinogen-like, and sedative effects similar to ketamine and zolpidem (**M&TX 7** at 7). The analysis concluded that lorcaserin produced some, but not all, of the positive subjective responses in the human abuse potential study when compared to zolpidem and ketamine. It also concluded that lorcaserin shared the hallucinatory behavioral profile of other 5-HT2 agonists. Nonetheless, HHS concluded based on the human abuse potential study that lorcaserin had a low abuse potential relative to Schedule III drugs and an abuse potential that is similar to Schedule IV drugs. DEA concluded that lorcaserin produces "subjective effects similar to those produced by zolpidem (Schedule IV) and ketamine (Schedule III)" (**M&TX 36** at 4).

In May 8, 2013, DEA rejected comments requesting lorcaserin be controlled in Schedules II or Schedule III based on it being an agonist at the 5-HT2A receptor **(M&TX 47** at 2). DEA stated that "placement in Schedule IV of the CSA will help restrict unsafe access to lorcaserin and reduce instances of its abuse" (**M&TX 47** at 2).

[4] As discussed above, some 5-HT2A agonists, such as mefloquine, are capable of producing hallucinatory effects and are not scheduled.

MDMA also offers a useful point of comparison on potential for abuse. As discussed above, between 1972 and April 1985, DEA took no action to schedule MDMA, despite encountering over 60,000 dosage units (**M&TX 44** at 6). DEA also documented clandestine laboratories that had produced or were capable of producing 10,000 dosage units and widespread availability of MDMA in Dallas, Texas. According to DEA, MDMA had been distributed in the Dallas area in 100 tablet bottles and had an established street market. The estimated street distribution of MDMA rose from 10,000 dosage units in 1976 to 30,000 dosage units per month in 1985 at the time of scheduling. To conclude that MDMA had a high potential for abuse, the DEA Administrator explained that the available scientific data showed that (a) MDMA produced physical and psychological effects in common with CNS stimulants like amphetamine and other hallucinogens (b) was similar in structure to MDA, a schedule I drug (c) had risk of producing neurotoxicity (d) was shown to have an abuse liability similar to cocaine and amphetamine, both substances with a high potential for abuse (e) was clandestinely produced and trafficked in the United States and (f) was used for its pleasurable effects. The Administrator repeated that the clandestine market for MDMA and potential neurotoxicity made it a serious risk to the public health and safety and met the standard for a high potential for abuse **(M&TX 44** at 8).

The Five Tryptamines at issue in this case do not show a high potential for abuse. The Five Tryptamines are far closer to lorcaserin (potential for abuse less than Schedule III) than MDMA (high potential for abuse). Unlike MDMA, I am unaware of any similar contemporary domestic market for any of the Five Tryptamines, let alone a market of 10,000 or more doses. They are not widely or easily available for purchase and are only available for purchase as research chemicals from reputable vendors. I also note that as part of its case for Schedule I, the

Government called more than a dozen witnesses as part of its case, many of whom specifically testified about actual abuse patterns.[5]

The Five Tryptamines neither show evidence of being addictive nor show signs of dependence.

5-MeO-MiPT

Tactogen is studying 5-MeO-MiPT and developing 5-MeO-MiPT derivatives precisely because it has effects that are said to be reliably distinct from those of LSD, DOM, DMT, and other well-known psychedelics. Specifically, at modest oral doses, 5-MeO-MiPT is reported to have prominent MDMA-like (entactogenic) emotional and interpersonal effects, few or only subtle perceptual effects (e.g., **GX15** at 599), and a potentially better side-effect profile than MDMA. Although 5-MeO-MiPT may partly overlap with LSD, DOM, and DMT in terms of pharmacological mechanisms, it is also meaningfully different from these classical psychedelics, which lack reliable MDMA-like emotional and interpersonal effects. No evidence suggests 5-MeO-MiPT is addictive or produces dependence. As discussed previously, there is a lack of case reports of toxicity after use of 5-MeO-MiPT, and, based on my exhaustive review, I do not believe there is sufficient evidence at the present time that would allow us to conclude that 5-MeO-MiPT has a high potential for abuse (as claimed in **GX 11)**. To the extent that 5-MeO-MiPT does have a potential for abuse, it most likely has a potential for abuse comparable to that of lorcaserin, which according to HHS and DEA, is less than drugs in Schedule III. All evidence suggests 5-MeO-MiPT could be safely administered to humans with medical supervision and that it could be used to enhance psychotherapy, as is being done with MDMA.

[5] The documents of the MDMA proceeding are available at: https://maps.org/1988/11/01/documents-from-the-dea-scheduling-hearing-of-mdma-1984-1988/. The witnesses called are available at https://maps.org/wp-content/uploads/1988/11/0003.pdf and https://maps.org/wp-content/uploads/1988/11/0027.pdf.

Fenfluramine

The example of fenfluramine further and clearly illustrates the limitations of the abuse liability evaluation procedures relied on by HHS and DEA for assessing the Five Tryptamines.

On July 19, 2022, DEA is publishing a proposal to remove fenfluramine entirely from the CSA based on a November 2018 petition submitted by pharmaceutical company Zogenix (now owned by UCB). (87 Fed. Reg. 42,979.) The action removes the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances. This publication follows a 2021 conclusion by HHS and FDA that fenfluramine does not meet the requirements for schedule IV or any other schedule.

DEA's treatment and analysis of fenfluramine and its conclusion that fenfluramine has "no potential" for abuse is inconsistent with its treatment of the Five Tryptamines. I note the following points:

1. The agency concluded that 177 seizures from January 1997 to November 2021 in 30 states and the District of Columbia. (87 Fed. Reg. at 42,983). HHS regarded this abuse to be "minimal" compared to the millions prescribed the drug. In contrast, the Eight Factor analysis prepared by DEA regards smaller numbers of law enforcement encounters with four of the Five Tryptamines as "large numbers" (**GX11** at 18).
2. The agency explained the available evidence suggests some individuals taking fenfluramine on their own initiative, without advice from a licensed medical practitioner, but not "to a meaningful degree." (87 Fed. Reg. at 42,982)
3. The agency explained "fenfluramine is a serotonin (5-HT) releasing agent" similar to MDMA and that "some drugs with the same mechanism of action are controlled in the CSA [ ] and some are not." (87 Fed. Reg. at 42,982)

4. The agency explained that in animal discrimination studies that fenfluramine fully generalized to the discriminative stimulus effects of serotonergic substances such as MDMA, quipazine, and MK-212. This highlights one of my main criticisms of the rodent discrimination studies relied on for the Five Tryptamines and why they are biased and unreliable: selective comparison. The tests relied upon for the Five Tryptamines did not do a discrimination test with drugs that affect brain functioning but lack abuse liability, such as antidepressants or antipsychotics. With fenfluramine, however, DEA notes that training drugs included quipazine and MK-212, which are not controlled substances.[6] In particular, the following paragraph concerns me (87 Fed. Reg. at 42,982):

> Drug discrimination assays in animals can be used to predict if a test drug will have abuse potential in humans. Although fenfluramine was first thought of as a stimulant based on its phenethylamine structure, fenfluramine does not generalize to stimulants when the discriminative stimulus effects were tested against a range of stimulant drugs. When rats were trained to discriminate fenfluramine from vehicle or other drugs, it became evident that fenfluramine produced discriminative stimulus effects similar to those of serotonergic substances such as quipazine and MK-212. HHS noted that fenfluramine fully generalized to drugs that do not have abuse potential such as lisuride, quipazine, and 1-(m-trifluoro-methylphenyl) piperazine (TFMPP), and generalized to some drugs that have abuse potential such as MDMA, but not to paramethoxyamphetamine (PMA, schedule I substance) or LSD (schedule I substance), which generalized to norfenfluramine. HHS concluded the drug discrimination studies are equivocal and do not provide clear evidence of the hallucinogenic effects of fenfluramine, a finding consistent with its clinical effects.

Based on fenfluramine fully generalizing to drugs that both do and do not have abuse potential, HHS concluded that the drug discrimination studies "are equivocal." Here, as I explained, the researchers never tested the Five Tryptamines against drugs that do not

[6] I also note that some research suggests, however, that quipazine produces a head-twitch response and other psychedelic-consistent effects (de la Fuente Revenga et al. Psychedelic-like Properties of Quipazine and Its Structural Analogues in Mice. ACS Chem Neurosci. 2021 Mar 3;12(5):831-844. doi: 10.1021/acschemneuro.0c00291 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7933111/).

have abuse potential. The failure to test comparisons with drugs that do not have abuse potential creates a bias in the results. Had such tests been conducted and shown full generalization, HHS would likely have reached the conclusion that the drug discrimination tests would have been "equivocal" for the Five Tryptamines and would not provide "clear evidence of hallucinogenic effects" consistent with current Schedule I compounds.

5. The agency noted that fenfluramine has activity on the 5-HT2A, 2B, and 2C receptors. (87 Fed. Reg. at 42,982).
6. The agency notes that, while fenfluramine was first thought of as a stimulant based on its phenethylamine structure, it does not generalize to stimulants when the discriminative stimulus effects were tested against a range of stimulant drugs and therefore, it "differs from other 5-HT agonists that are phenethylamines." DEA's statement confirms similarity in chemical structure or membership in a class of compounds does not necessarily translate to pharmacological similarity to other compounds in the class. (87 Fed. Reg. at 42,984).

Advancement of Psychedelic Science

It is my opinion that the scientific understanding of psychedelics and related compounds has developed considerably in the past decade. In particular, older scientific frameworks fail to properly account for the abuse potential. The science on psychedelics from the 1970s is now outdated as it was based on a small number of compounds and limited methods of making scientific measurements. In the last few years, scientists have improved both tools for measuring and manipulating both neural activity in animals and biological activity inside cells as well as tools for simulating interactions of drugs with receptors and enzymes.

It is my opinion that over the past decade, the science and understanding of psychedelics—as well as the science surrounding 5-HT2A serotonin agonists—has developed considerably. Carhart-Harris and Goodwin refer, for example, in 2017, to a "hiatus" of psychedelic research and a "present revival" (**M&TX 12** at 1). Citing research largely from the past 12 years, they explain this revival has been built on a "foundation of human neuroimaging" and "psychopharmacology studies with psychedelics" (**M&TX 12** at 1).

It is my hope that the regulatory approach taken by DEA can also develop and incorporate the legitimate public interest in improved medicines into their evaluation of these compounds.

I certify under penalty of perjury that the foregoing is true and correct.

Executed on 7/19/22

Matthew Baggott, PhD