

“Synthetic Drugs, Real Danger”

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Committee on the Judiciary  
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\*The views expressed here are my own and not those of any institution with which I am now or have previously been affiliated.

Chairman Sensenbrenner, Ranking Member Jackson Lee, and Members of the Committee, thank you for the opportunity to appear today.

I wish to highlight three overarching themes in what I shall present. The first is that placing substances into Schedule 1 presents barriers to research and discovery of potential new therapeutics; second is that drug scheduling should be driven by the best science and evidence of actual abuse, and not guessing; and finally that in any new legislation we would hope to avoid creating schedules of compounds for which there is no evidence of harm to human health and leading to increasing the incidence of incarceration we have witnessed as a result of the drug war.

For most of my professional career, going back to my graduate training, I worked with a variety of what are now called synthetic drugs, and possessed a Researcher's Schedule 1 Drug Enforcement Administration (DEA) registration for many different kinds of abusable substances. My primary research goal was to understand how the structure of a molecule allowed it to engage a biological target, usually in the brain, which led to a better understanding of the brain mechanisms of action for these substances. I pursued significant research with psychostimulants such as substituted amphetamines, MDMA (ecstasy), and various hallucinogens, including LSD, mescaline, psilocybin, and numerous synthetic molecules. The type of work I did is called structure-activity relationship (SAR) studies, which requires working with a variety of different types of molecules to determine what structural elements they may have in common.

Let me state at the outset that I am very concerned about the potential harms to human health that can be presented by new "synthetic drugs". Sadly, I am acutely aware of the problem because some of my own research publications were mined by unscrupulous persons for illegal purposes

and economic gain. It is very clear to me that the use and availability of these substances requires some kind of response, including regulation. Yet, I have seen nothing in the proposed legislation that would have prevented the recent rapid emergence of synthetic cannabimimetic compounds, such as those incorporated into so-called Spice mixtures. Rather, the proposed legislation is focused on expanding the chemical landscape around previously known controlled substances. Considerable thought needs to be given to reasonable approaches to controlling completely new chemotypes of synthetic substances, beyond those we already know about.

The real question is what the nature of that response should be, so that legitimate needs for researchers can be preserved, while still being able to stem the flow of dangerous synthetic chemicals. I believe that an appropriate response should include an examination of the following three policy questions: first, what barriers to research examining potential therapeutic uses for a substance will be created by scheduling that substance; second, how rigorously is science and best evidence guiding the development of drug scheduling legislation and policy decisions on this issue; and three, what impact will drug scheduling legislation and policy decisions on this issue have on mass incarceration, especially in cases where substances that have not even been fully vetted by the scientific community for possible dangers to human health (i.e. when we don't know for certain that the substances proposed for scheduling will actually have abuse potential or addiction liability) have been added to a drug schedule.

### **Drug Control Should Not Undermine Research**

As an example, for about a decade I had a grant to study how MDMA worked in the brain, but a secondary focus of my work was to identify possible new analogues of MDMA that might have therapeutic potential. At a certain point it became clear that there was no interest in funding the

latter type of research, but only in understanding why MDMA seemed to cause neurodegeneration in rodents. I ended my research on MDMA analogues at that point.

In my experience, when a compound is placed into Schedule 1, very few investigators are interested in pursuing research with it, except in certain specific instances. Barriers to researching Schedule I substances are a driving factor for this lack of engagement. Obtaining a Schedule 1 license is not a trivial matter. A researcher first of all has to have a reason or motivation to obtain the license. In most cases today it will be to study the deleterious properties of a specific drug of abuse, to understand how and why it negatively impacts the health of an individual. Federal institutes such as NIDA usually fund these studies, and many biomedical scientists follow these avenues of research.

By contrast, there is currently no Federal funding available for research that could identify *beneficial* properties of a Schedule 1 substance, with the possible exception of recent studies of medical marijuana. In these cases, the investigator must have a strong personal belief that something useful will be discovered by their research that is of sufficient importance to justify the regulatory demands of a Schedule I license. To wit, a researcher must submit an application to the DEA that includes the investigator's scientific credentials, the description of the laboratory, a precise description of the work to be carried out, listing the specific substance to be used, and a calculation of how much substance will be needed and for how long. If the DEA determines that the request for license is justified, there is then an inspection of the storage facility the investigator will use, to ensure that the controlled substance cannot be easily diverted, in some cases involving the purchase of a heavy safe by the investigator or their institution and/or enhanced security procedures. Inventory and use must be documented, and there is a license fee for most non-public institutions. In addition, unlike Schedules II-V of the CSA, a

schedule 1 license must be obtained for a specific chemical entity. If an investigator wishes to work with additional Schedule 1 substances, a separate application or amended application must be submitted. All of these costs and regulatory burdens can be onerous, especially for academic investigators with lean research budgets.

These requirements are not waived or reduced if the investigator plans to use amounts of controlled substance that do not represent a significant potential for diversion. For example, mescaline is a hallucinogen with a human dose in the range of 200-400 mg. If an investigator wishes to carry out mouse studies with mescaline, they might typically require only 20-30 mg, much less than a single human dose. Yet, the Schedule 1 license application process and storage requirements remain the same as if the investigator was requesting to use several grams of the substance. That is not an extreme case, as many studies today can be carried out in cells, which might require only a few milligrams of a controlled substance. In the laboratory where I currently work, there is a large drug screening facility funded by the NIMH. Recently, the laboratory director was asked whether he could screen a large number of new synthetic substances, analogues that had recently been scheduled, but for which very little pharmacology was known. Even though such screening would involve only a few milligrams of each substance, he was forced to decline the request because he did not have a Schedule 1 license for each new compound that needed to be screened. That is an issue that certainly bears some consideration in developing any new legislation.

Pharmaceutical companies today often search for novel therapeutic actions in large, cell-based assays, generally referred to as High Throughput Screens (HTS). However, they generally will not include controlled substances or controlled substance analogues in their screening libraries

because a license would be required to include each specific compound in the library, despite the fact that the amounts of controlled substances involved in HTS are miniscule.

Why is research involving Schedule I drugs so important? Let me begin answering this question by noting an area of historical interest that is relevant to the discussion here today. In the 1950s and 1960s there was widespread recreational use of hallucinogens such as LSD and psilocybin, ultimately leading to the Controlled Substances Act of 1970. Despite numerous anecdotal reports of therapeutic effects of these substances, the 1970 law led to a virtual cessation of all clinical research with LSD, psilocybin, or similar Schedule I substances. Yet, in the past decade, several small pilot and Phase 2 clinical studies have been completed both in the U.S. and in Europe, which indicate that psilocybin may have unique therapeutic efficacy in treating anxiety, depression, and addiction to alcohol and nicotine, after only one treatment.

If these early results can be confirmed in larger Phase 3 studies, it will be a major therapeutic advance for psychiatry in treating these, and other very difficult to manage conditions. These pilot and Phase 2 clinical studies were not supported by any government agency, but rather as a result of the personal commitment of a small number of scientists and clinicians who believed that early clinical studies of hallucinogens had been flawed, and that perhaps new and better designed clinical experiments might finally reveal whether hallucinogens actually possessed any medical benefit. Indeed, in 1993 I was a founder of a small not-for-profit research institute that supported these studies. In the absence of Federal agency support, a number of philanthropists became convinced by our rigorous approach to science that these studies were worthy of support. The committee will recognize that this approach took substantial personal commitment, as it ran counter to conventional wisdom and lacked access to significant institutional funding. In effect,

Schedule I designation has hindered this potential advance in medicine for more than four decades, and continues to hinder additional research.

As a second example, consider the case of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy), a Schedule I drug. Commonly used at dance parties and raves worldwide for the past several decades, recent Phase 2 clinical studies have demonstrated that MDMA, coupled with psychotherapy has remarkable efficacy in treating the symptoms of PTSD, a common psychiatric disorder in many hundreds of thousands of U.S. war veterans. Here again, if validated with planned larger Phase 3 clinical studies, this finding may represent a revolutionary new and much needed treatment for PTSD that sprang from a synthetic Schedule 1 chemical that was widely abused and also difficult to study because of Schedule I requirements. In this example, my laboratory was able to synthesize a sufficient amount of high-quality MDMA for clinical work prior to it actually being placed into Schedule 1. Had MDMA been scheduled more quickly, my laboratory would not have been able to produce it, and is unlikely that today we would have the possibility for this new treatment for PTSD. The investigator who we prepared the MDMA for had already requested bids for the synthesis of the substance from chemical synthesis companies, but they were far in excess of the cost his not-for-profit organization could afford. In fact, in the two other collaborative projects where I was able to produce Schedule 1 substances (i.e. DMT and psilocybin), again, no chemical synthesis firm was willing to produce a sufficient amount of material in a quantity and quality that could be used in human studies, at a cost the investigators could afford.

Some of the most difficult to treat diseases we face today involve dysfunction in the central nervous system. Unfortunately, most major pharmaceutical companies have abandoned research on novel drugs to treat conditions such as depression, bipolar disorder, obsessive-compulsive

disorder, and others. These diseases have unknown causes, and the research is extremely expensive, with only a low probability of success. Yet the very kinds of substances that we are concerned with here today act in the brain, often by unknown mechanisms, and it is quite possible, as was the case with MDMA, that unexpected therapeutic efficacy might be found upon researching some of them. I am very concerned that new regulations do not, to use the old axiom, “throw out the baby with the bath water.”

As another relevant example, when my son Charles Nichols was a new Assistant Professor of Pharmacology at the LSU medical center in New Orleans, he wished to carry out a study with a hallucinogen type molecule, but he had not yet obtained his Schedule 1 license. He asked me if there was such a molecule that was not controlled. There was only one, called DOI. It is the only molecule in this drug class that has not been scheduled, because it is the only tool that neuroscientists can still obtain without a Schedule 1 license to study the receptor target for hallucinogens. Using DOI he discovered, quite by accident, that it had unprecedented and potent anti-inflammatory properties, and his most recent research suggests that hallucinogens may be efficacious in treating cardiovascular disease as well as a variety of inflammatory conditions, including arthritis. His findings represent a potential major breakthrough for treating these conditions because current therapies either lack suitable efficacy, or else others, such as the biologics, are extremely expensive. Serendipitously, he had discovered a new potential pathway for reducing inflammation, including the possible prevention of asthma, only because that particular hallucinogen had not been placed into Schedule 1. Had it already been scheduled, he likely never would have discovered these new therapeutic applications.

The cost of pharmaceutical research and development is already very high, and any additional regulatory burdens, such as working with controlled substances or their analogues, even as



manufacturing intermediates, will be a strong disincentive to using them. The administrative and regulatory burden associated with conducting research using Schedule I drugs is a significant disincentive that would prevent pharmaceutical companies and researchers from exploring the value of these compounds. If a new drug molecule is discovered to have pharmacological properties that would likely lead to its being placed into Schedule 1, that finding usually signals the end of research on that drug.

It is difficult to convince agencies and investors to support research with unknown, novel substances; neither drug companies nor researchers want to deal with DEA/Schedule I requirements. It is simply easier for investigators to pursue studies that can be funded by institutions and government agencies. In addition, specialty chemical suppliers generally have little if any interest in producing any substance that is in Schedule I. Many of the recent clinical studies of MDMA, DMT, and psilocybin obtained their high-purity substances from synthesis in my laboratory under DEA-approved collaborative arrangements. Few, if any, laboratories and lab directors have the experience, proper licensing, and personal motivation to produce sufficient amounts of schedule 1 substances suitable for clinical studies at cost of production. Although the National Institute on Drug Abuse (NIDA) can provide small amounts of controlled substances to qualified and licensed investigators, their mission is to prevent drug abuse. Hence, they generally support studies designed to identify harmful effects of drugs, rather than research that is geared toward identifying beneficial properties of controlled substances.

When a substance is determined to be an analogue of a scheduled controlled drug, any research being conducted with that substance must stop until DEA licensing can be obtained to continue working with the newly controlled substance. Analogue designations have a direct impact on research.

I am particularly concerned that broad scheduling of compounds with no history of abuse or evidence of abuse potential, even in animal or in vitro models, will lead to control of compounds that also may be important intermediates for manufacture of medicinal agents. Regulations concerning use of controlled substances is an obstacle not only to their production as final compounds, but also their use in legitimate manufacturing processes. These controls are a disincentive to their use because they involve licensing fees, strict inventory control, and enhanced security procedures.

I believe that any legislative response to synthetic drugs must keep in the mind the challenges that scheduling presents for legitimate research, including possible research that might lead to discovery of novel therapeutic agents. I think these issues should involve discussions with representatives for numerous stakeholders, including academic and institutional scientists, as well as pharmaceutical manufacturers and enforcement agencies, so as to lead to a balanced approach to control that minimally impedes legitimate research.

### **Drug Control Should Be Grounded in Science**

Federal drug scheduling law has given law enforcement and principally the DEA – not scientific experts or health officials – the authority to make final decisions about how a new substance should be scheduled. In the past the sudden appearance of a new psychoactive substance on the underground market has triggered the research and inquiry necessary to determine that the new substance represents a threat to human health, ultimately leading to its scheduling and control. It is my understanding that agencies within HHS, specifically FDA and NIDA are tasked with making recommendations to DEA regarding scheduling decisions. Their recommendations are based on a variety of factors, which include evidence that the purported compound was actually

what was ingested, as demonstrated by chemical analysis and determination of plasma levels of the drug, as well as specific pharmacological tests showing potential for abuse, including for example, such tests as binding and functional activity at the relevant brain receptors, animal models of drug-self administration, drug discrimination tasks, and others. These agencies use the best science available to make a recommendation to DEA. These divisions also assess whether or not the new substance is actually causing harm to human health. These and other factors play into the recommendation FDA and NIDA makes to DEA regarding whether or not to place a new compound into schedule 1. Superficial comparisons of chemical structure resemblance or expected/predicted pharmacological effects are not a sufficient basis to place a compound into Schedule 1.

In the absence of these sorts of assessments, whether in human, animal, in vitro tests, or others, I believe it is unwise to propose scheduling novel molecules. No one can predict the potential of a new, untested molecule. It may have effects in humans similar to other structures, it may have completely novel effects, or it could be completely inactive. Sometimes changing a single atom on a molecule can dramatically alter its pharmacology. For example, adding one bromine atom to the potent hallucinogen LSD virtually abolishes its hallucinogenic activity. Prior to experimental studies showing that effect, no chemist could have predicted that dramatic change in biological action. Similarly, changing one methyl group on morphine to a three-carbon allyl group gives nalorphine, a drug that can actually block the effects of morphine. I also might note that bupropion (Wellbutrin) an effective antidepressant agent, can be considered to be a cathinone analogue, yet it has no abuse potential. My real point here is simply to emphasize that prediction of pharmacological properties based on superficial structural comparisons is not a

reliable way to discern whether a new molecule will have abuse potential or will present a harm to human health.

As a perhaps more contemporary example, about 15 years ago it was discovered that ketamine, a dissociative anesthetic with significant abuse potential and addictive qualities, can produce rapid and virtually immediate antidepressant properties that last for up to about one week in some individuals. Yet, earlier this month, in the highly respected scientific journal *Nature*, it was reported that the antidepressant effect of ketamine is probably due to its metabolite 2-hydroxynorketamine, which does not produce hallucinogenic effects. Only experimental science could reveal that, yet the proposed new bills would likely have encompassed this metabolite as a proposed ketamine analogue, and would have led to its scheduling. Currently a ketamine analogue known as methoxetamine has been the subject of some abuse and has been scheduled in several states, yet with some anecdotal reports that it too may have novel antidepressant properties. New legislation that would broaden the definitions of analogues would likely lead to scheduling of a number of ketamine analogues, despite the possibility that legitimate clinical research might reveal novel antidepressant properties for one or more of them.

It is imperative therefore, that placing new substances into Schedule I must be based on solid scientific evidence; the possibility of preventing access to the molecule for research or potential therapeutic applications is too big a price to pay for a suspicion that a previously unknown molecule *might* have abuse potential.

Thus, it is important for any final scheduling decision to reflect a balance between law enforcement priorities and the scientific knowledge around these compounds. When scheduling decisions are being made, scientific and health experts both inside and outside of the government

should have a formal role in deciding the appropriate schedule for an emerging substance, and if the substance has not formally emerged as a potential danger to human health, the suspicion that it might emerge does not seem sufficient to me to warrant scheduling.

Scheduling decisions should always be based upon science and available evidence. There should be a clear and compelling set of scientific criteria used to assess whether a particular substance should be controlled. There are literally many hundreds of thousands of synthetic compounds that could be made, many of which exist as “tweaked” versions of another similar compound. The scientific community as of yet knows very little about many of the most recently produced compounds, their pharmacology, abuse potential, or therapeutic potential. Under the federal Controlled Substances Act, there are no schedule categories for drugs that have no known medical value but also have not been proven to have high abuse potential, such as various hypothetical synthetic drugs. We should carefully assess compounds flagged by law enforcement, being sure to add only compounds with demonstrated psychoactive properties and a risk profile that clearly points to a public health and safety risk.

Compounds that have no demonstrated potential for abuse, let alone demonstrated psychoactive properties, should not be added to Schedule I. Doing so arbitrarily makes these compounds much more difficult to research. We must be careful not to sweep compounds into Schedule I that ultimately might be found to have therapeutic or scientific value, with all the ensuing red tape that can deter promising research.

### **Drug Control Should Not Exacerbate Mass Incarceration**

Another reason for due diligence within the scientific/medical community is to ensure that compounds with no demonstrated abuse potential or real danger to public health are added to the

drug schedule is to take into consideration the potential of needlessly prosecuting and incarcerating people for using or possessing these substances. Logic should tell us that the harms caused by enforcement of drug laws should not be more serious than the drugs themselves. Although individuals who knowingly manufacture and distribute substances that harm human health should be held accountable (ignoring the harms of alcohol and tobacco), I and many others do not believe that making criminals of users for simple possession is the appropriate approach. There appears to be a developing consensus that use of psychoactive substances should be approached as a public health issue, rather than a criminal one.

The current “war on drugs” has been largely unsuccessful in combatting drug use and has contributed to the United States having the largest prison population in the world, a large percentage of whom were incarcerated as a result of nonviolent drug offenses. Compounds that have demonstrated harm to human health, and those who manufacture and distribute them should be the focus of enforcement, not hypothetical compounds that some believe may cause harm, but without good scientific evidence.

## **Conclusion**

In summary, I strongly agree that the proliferation of new psychoactive substances represents a great threat to the health of our youth, and regulation must be a component of the solution to this problem. I also believe, however, that drug control should be grounded in good science, and that experts in the areas of medicinal chemistry, neuropharmacology and toxicology should be involved in decisions about which compounds to schedule. There needs to be balance between the needs of research and enforcement, so that potential new therapies are not lost by restricting access to novel compounds. I do not believe that current proposals to expand the chemical

landscape around already-known synthetic substances will be an adequate solution when completely new synthetics emerge that have not previously been encountered, such as the synthetic cannabimimetics. Finally, I do not believe it serves a useful purpose in society to impose harsh penalties on those who are found to be in possession of amounts of controlled substances for personal use; harms from law enforcement should not be greater than the harms resulting from use of these substances. Adolescents are known to be curious and to experiment, and most pass through that phase without serious consequences. Laws that impose draconian penalties and felony convictions on such persons destroy their future as productive American citizens. The focus needs to be on manufacturers and traffickers of dangerous substances.