UNITED STATES DEPARTMENT OF JUSTICE

Drug Enforcement Administration

In the Matter of **Schedules of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I**	**Docket No. 22-21**

ORDER FOR PREHEARING STATEMENTS

On April 11, 2022, the Drug Enforcement Administration ("DEA") published a Notice of Proposed Rulemaking with docket number DEA-824[1] and titled "Schedules of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I." 87 Fed. Reg. 21,069 (2022). The Notice of Proposed Rulemaking also provided a May 11, 2022 deadline for requests for a hearing ("RFH"), but did not set a hearing location. *Id.* at 21,069.

On April 27, 2022, Panacea Plant Sciences ("Panacea"), acting *pro se*,[2] filed a document titled "Regarding Docket No. DEA-824" ("Panacea RFH"), regarding the proposed placement of DOI and DOC in Schedule I of the Controlled Substances Act. In its filing, Panacea specifically requests a hearing. Panacea RFH at 5.

In its filing, Panacea indicated that it is a "Washington State biotech company" and set forth its reasons why it opposes DEA's proposed action. Panacea RFH at 1. Panacea did not serve its RFH on the DEA Office of Chief Counsel ("the Government"), but requested that the RFH be shared with "(1) Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn:

[1] For purposes of these administrative proceedings, all filings shall be captioned as shown above with the Matter title and Docket No. 22-21.

[2] In accordance with 21 C.F.R. § 1316.50, which is made applicable to the instant proceeding pursuant to 21 C.F.R. § 1308.41, Panacea is advised that it has the right to seek representation by a qualified attorney at its own expense. Representation options should be explored and finalized as expeditiously as possible.

Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (3) Drug Enforcement Administration, Attn: DEA FR Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152." *Id.* at 5.

On May 10, 2022, Elijah Z. Ullman filed a document, acting *pro se*,[3] with the subject "Notice of Appearance."[4] The filing did not specifically request a hearing and it is unclear if Mr. Ullman intended the filing to also serve as a Request for Hearing. In his May 10, 2022 filing, Mr. Ullman provided information indicating why he believes the DEA should not place DOI and DOC into Schedule I. Notice of Appearance at 2-3. Mr. Ullman also recommends that DEA maintain the non-scheduled status of DOI and DOC to expedite research. *Id.* at 4. Mr. Ullman further recommends that the DEA "[e]stablish a new framework to remove Schedule 1 DEA licensing requirements for any laboratories with a Schedule II license, allowing them to study Schedule 1 substances." *Id.*

I am the Administrative Law Judge assigned to hear the above-captioned matter.

To the extent that Mr. Ullman intended his filing to also serve as a Request for Hearing, he is hereby **ORDERED** to file such a document, complying with 21 C.F.R. §§ 1308.44, 1316.47, no later than **May 31, 2022**.[5]

Upon consideration of Panacea's RFH, and to the extent that Mr. Ullman files a RFH,[6] it is hereby **ORDERED** that the Government file a Prehearing Statement no later than **2:00 p.m. Eastern Time ("ET")/11:00 a.m. Pacific Time ("PT")** on **June 13, 2022**. A copy of Panacea's

---

[3] In accordance with 21 C.F.R. § 1316.50, which is made applicable to the instant proceeding pursuant to 21 C.F.R. § 1308.41, Mr. Ullman is advised that he has the right to seek representation by a qualified attorney at his own expense. Representation options should be explored and finalized as expeditiously as possible.

[4] Mr. Ullman indicated that Daniel J. Lustberg and Lindsey Galbo will also appear in this matter.

[5] Absent advance leave by this tribunal on a motion supported by good cause, all filed documents (other than noticed proposed exhibits offered by either party on the merits) shall be limited to fifty (50) pages (utilizing 12-point characters and 1-inch margins). All filed documents shall be **signed** (electronic signatures acceptable) by the person filing the document and the **pages shall be numbered**.

[6] Panacea and Mr. Ullman shall be referred to as "the Interested Persons." *See* 21 C.F.R. § 1308.44(a)("Any interested person desiring a hearing on a proposed rulemaking shall . . . file a written request for a hearing . . . ."); *see also* 21 C.F.R. 1300.01 ("Interested person means any person adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811)" and "Person includes any individual, corporation, or governmental subdivision or agency . . . or other legal entity.").

RFH is provided as Attachment A. A copy of Mr. Ullman's Notice of Hearing is provided as Attachment B.

It is further **ORDERED** that Panacea file, and to the extent that Mr. Ullman files a RFH that he also file, a Prehearing Statement no later than **2:00 p.m. ET/11:00 a.m. PT** on **July 12, 2022**. The parties' Prehearing Statements must be served on each other and contain the following sections:

1. **Issue(s).** Statement of the perceived issues.
2. **Requested Relief.** Statement of the relief requested.
3. **Stipulations.** Proposed stipulations and admissions of fact. Each party is directed to examine available evidence and determine which facts may be the subject of stipulation to narrow the issues to those that will be and should be the subject of contested litigation.
4. **Witnesses.** Names and *current* addresses of all witnesses whose testimony is to be presented. The Interested Persons should note that if an Interested Person, or a representative thereof, intends to testify, that person must be listed as a witness, and a summary of that person's testimony as described below must be provided.
5. **Summary of testimony.** Brief summary of the testimony of each witness. *The summaries are to state what the testimony will be, rather than merely list the areas to be covered.* The parties are reminded that testimony not disclosed in the Prehearing Statements or pursuant to subsequent rulings is likely to be excluded at the hearing.
6. **Documents.** A list of all documentary evidence, including affidavits and other exhibits to be offered in evidence, specifying the number of pages in each. Each exhibit is to be numbered or lettered ("For Identification") with the designation to be used at the hearing.
7. **Position regarding hearing situs.** Statement of position regarding the location where the hearing will be conducted.[7]
8. **Other matters.** Any other matters that the parties consider relevant.
9. **Best estimate as to time required for presentation of own case.**

[7] The current COVID-19 pandemic may impact the setting of venue in this case, and may result in the hearing being conducted in whole or in part through the use of videoconference ("VTC") technology.

It is further **ORDERED** that **a Prehearing Conference in this matter will be conducted by video teleconference ("VTC")** on **July 19, 2022, at 1:00 p.m. ET/10:00 a.m. PT**;[8] and it is further **ORDERED** that all proceedings will be governed by the provisions of 21 C.F.R. §§ 1316.41-1316.67, which are made applicable to this proceeding pursuant to 21 C.F.R. § 1308.41.[9] Your attention is specifically directed to 21 C.F.R. § 1316.45, which provides, *inter alia*, that "[d]ocuments shall be dated and deemed filed upon receipt by the Hearing Clerk." Documents (other than proposed exhibits) may be filed electronically, by hard copy, or by facsimile with a hard copy follow-up on all facsimiles. Only one method of document filing may be utilized.

Electronic Filing: The preferred method of filing correspondence in these proceedings is as a PDF attachment via email to the DEA Judicial Mailbox (**ECF-DEA@dea.gov**). The forwarding email on all electronically filed correspondence must indicate that it was simultaneously served on the opposing party via email. All parties must ensure that all documents filed with the DEA Judicial Mailbox are simultaneously served on the Government Mailbox at (**dea.registration.litigation@dea.gov**). Any request(s) to modify email addresses of a party or counsel must be made on notice to this tribunal and the opposing party. The email receipt date reflected by the DEA Judicial Mailbox server shall conclusively control all issues related to the date of service of all filed correspondence, provided however, that correspondence received after 5:00 p.m., local Washington, D.C. time, will be deemed to have been received on the following business day. Note: While email is utilized as the method to forward documents for filing—as attachments—no substantive matter communicated through the body of a forwarding email will be considered. The parties are directed to refrain from including social security numbers or personally identifiable information in electronically-filed documents. Proposed exhibits will not be accepted via electronic filing.

Hard Copy and Facsimile Filing: Alternatively, correspondence may be filed in hard-copy form. Hard-copy filings must be served in triplicate and addressed to my attention at: **DEA**

---

[8] Logistical issues (including parties' availability) will be coordinated by Law Clerk Courtney Lutz, who can be contacted at (571) 362-7030 and Courtney.J.Lutz@dea.gov. To access the VTC Prehearing Conference, the respective parties will receive an evite to the email addresses of record in this case.

[9] Additional helpful information regarding DEA administrative proceedings may be found at the OALJ website, https://www.dea.gov/administrative-law-judges.

Office of Administrative Law Judges, 8701 Morrissette Drive, Springfield, VA 22152.
Because the DEA Hearing Facility is not physically collocated with the DEA mailing address, hard copy filings must be posted sufficiently in advance of the due date to assure timely receipt by this office. Documents may also be served via facsimile,[10] so long as they are followed up by hard copies consistent with the directions above that are simultaneously placed for delivery. Facsimile filings will be deemed timely if received at this office by the date and time due, and are limited in size to twenty (20) pages, absent prior permission granted by me upon advance request.

Failure to timely file a prehearing statement that complies with the directions provided above may result an implied withdrawal of a request for hearing. Prehearing statements should not include motions, which should be filed separately.[11]

It is further **ORDERED** that any requests for extension of time to file must be made by written motion sufficiently in advance of scheduled deadlines to be considered and ruled upon.[12]

Dated: May 18, 2022

PAUL SOEFFING
Digitally signed by PAUL SOEFFING
Date: 2022.05.18 13:49:00 -04'00'

PAUL E. SOEFFING
U.S. Administrative Law Judge

[10] The facsimile number for this office is (202) 307-8198.
[11] A prehearing ruling setting deadlines will be issued after the prehearing conference.
[12] Filing deadlines are adhered to strictly. In the event a document is filed untimely, without an approved extension of time granted in advance by this tribunal, the untimely filing must include a separate Motion for Leave to file the untimely document and such Motion for Leave must include a statement of good cause for the late filing. Documents that are submitted for filing untimely will be accepted for filing at the discretion of the tribunal if good cause is shown.

CERTIFICATE OF SERVICE

This is to certify that the undersigned, on May 18, 2022, caused a copy of the foregoing to be delivered to the following recipients: (1) Paul Dean, Esq., Counsel for the Government, via email to the DEA Government Mailbox at dea.registration.litigation@dea.gov; (2) David Heldreth, CEO of Panacea Plant Sciences, via email at davidh@panaceaplantsciences.net; (3) Elijah Z. Ullman, via certified First-Class U.S. Mail, return receipt requested, at:

Elijah Z. Ullman
1063 Burton Drive NE
Atlanta, Georgia 30329

BELLA MAPESO

Digitally signed by BELLA MAPESO
Date: 2022.05.18 13:55:52 -04'00'

Bella A. Mapeso, Staff Assistant
Office of Administrative Law Judges

Attachment A

Panacea
Plant Sciences

Regarding Docket No. DEA-824

To Drug Enforcement Administration,

Panacea Plant Sciences is writing in regards to: "Docket No. DEA-824" which is titled "Schedules of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I" Panacea Plant Sciences would like to provide comment and information in opposition to the following proposed actions by the DEA.

The DEA is trying to place these items into schedule 1:

- 2,5-dimethoxy-4- iodoamphetamine (DOI),
- 2,5-dimethoxy-4-chloroamphetamine (DOC),

Panacea Plant Sciences is a Washington State biotech company which conducts research and works with groups that conduct research which utilizes 2,5-dimethoxy-4- iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) as these are common compounds utilized in the research of psychedelic mechanisms and medical benefits. If the DEA schedules these items it will require our company to become licensed by the DEA for these items which will cost our company thousands of dollars in application fees and thousands more in related requirements. As such we are an interested party with standing to challenge the DEA actions to control/schedule these items as outlined in "Docket No. DEA-824".

Medical Uses

At the moment hallucinogens/psychedelics are having a revival for their use as medical treatments. This is due to the apparent connection between 5-ht2a agonism and the ability to provide long term relief from and treatment of depression, anxiety, addiction, PTSD and other mental health conditions.-5ht2a receptor agonism has been identified as a primary mechanism of medical benefit. As such it is intriguing to see the DEA document in the docket which uses the 5ht2a activity and binding levels used as reasons to make these compounds illegal. This same activity is precisely *why* these compounds do, in fact, have medical uses.

Until recently, psychedelic/5ht2a agonist compounds such as LSD, mescaline, psilocybin and DMT have been ruled schedule 1 and thus having no accepted medical benefit. However, as mentioned above, 5ht2a agonists, including the compounds listed here, have now been established to definitely have medical benefit. The same DEA, FDA and NIH are currently allowing and hosting/funding medical trials which have already shown medical benefits of using

LSD, mescaline, DMT and psilocybin. And additionally for DOI and DOC which due to their long lifespan are being studied for use as asthma treatments.-
https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.2018.32.1_supplement.830.3

The FDA has given Compass Pathways breakthrough treatment status for the 5ht2a agonist psilocybin:
https://compasspathways.com/compass-pathways-receives-fda-breakthrough-therapy-designation-for-psilocybin-therapy-for-treatment-resistant-depression/

Another company, mindmed, is working with the FDA for LSD, another 5ht2a agonist, as a medical treatment:
https://www.prnewswire.com/news-releases/mindmed-provides-status-update-on-ind-for-phase-2b-trial-of-lsd-for-the-treatment-of-generalized-anxiety-disorder-301448831.html

Another company is working with the FDA for a DMT IND and medical treatment:
https://www.biospace.com/article/releases/algernon-pharmaceuticals-receives-positive-feedback-from-u-s-fda-for-psychedelic-drug-dmt-clinical-research-program-for-stroke/

Our understanding is that if a compound specifically is being studied for medical use then it should NOT qualify for schedule 1 status as that is reserved for compounds with no known medical use. Similarly this data would further indicate that no psychedelic compound should be in schedule 1 as the entire class of drugs is being investigated for their method of action being key to providing mental health treatments. It would seem unacceptable and disingenuous for the DEA/FDA to approve medical trials using 5ht2a agonists and then ask for the compounds to be placed in schedule 1, which would ultimately hinder future medical research and clinical applications.

Panacea Plant Sciences is currently studying DOI and DOC along with other similar compounds in order to develop treatments for conditions like depression, anxiety, post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) and also to study how these conditions work.

Lack of Dangers

Deaths attributed to these compounds have only occured with comorbid use of other drugs and the identified phenethylamines. As such it is likely that these deaths have very little to do with the phenethylamines alone and are either directly due to the use of alcohol and psychiatric medications which present a known danger or from the combination of those items with the drugs. Tee single case of a death labeled as DOC alone actually simply states that DOC was present in the toxicological findings and that the person died from pulmonary edema and a subgaleal hemorrhage on the right parietal scalp, but also indicated that the user was a known user of methamphetamine and also the site of death contained kratom and other drugs. There is no direct correlation to confirm that the injuries which caused death are actually the cause of the death as these injuries are also frequently found in long term methamphetamine users. As such there is not a single death which can be directly attributed to these substances. Due to these

facts we find fault with the HHS, FDA, DEA and related government findings of dangers or risk of death as conjecture and not based in fact.

Additionally the doses and purity of the drugs used by the affected individuals was unknown. These factors which led to unknown drug dosing and the polydrug use are due to lack of education and transparency associated with the drugs' prohibition for human use under the Federal Analogue Act of 1986. As such the public cannot share information directly and openly about their drug use, which exacerbates unsafe drug use. These compounds have only been encountered a few hundred times by law enforcement vs thousands of daily encounters for other compounds. The attributed risk and dangers are overblown by DEA analysis.

Additionally there is little diversion risk from research and development of these compounds. DEA documents directly state the finding that companies conducting research are NOT involved with the diversion into recreational or related markets.

"DEA further notes that DOI and DOC are available for purchase from legitimate chemical companies because they are used in scientific research. No evidence of diversion is apparent from these companies. As such, this characteristic of abuse potential is not applicable"

Federal Analogue Act

The DEA is expressing the view that it is necessary to place these items into schedule 1 in order for the DEA in order to reduce the risk to the public and due to lack of medical uses. However, as we describe above these compounds do have medical uses and the risks are actually due to the illegal or unregulated nature of the compounds and due to use of alcohol and other medications with them, NOT due to the compounds themselves. Additionally, any recreational use of the compounds or sales for unregulated human use are ALREADY illegal and already within the jurisdiction of the DEA and law enforcement without need to move them into schedule 1. This is due to the fact that the compounds fall under the definitions included in the analog act.

Under the Federal Analogue Act:

- (A) Except as provided in subparagraph (C), the term controlled substance analogue means a substance -
    - (i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;
    - (ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or
    - (iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II.

- (B) The designation of gamma butyrolactone or any other chemical as a listed chemical pursuant to paragraph (34) or (35) does not preclude a finding pursuant to subparagraph (A) of this paragraph that the chemical is a controlled substance analogue.
- (C) Such term does not include -
    - (i) a controlled substance;
    - (ii) any substance for which there is an approved new drug application;
    - (iii) with respect to a particular person any substance, if an exemption is in effect for investigational use, for that person, under section 355 of this title to the extent conduct with respect to such substance is pursuant to such exemption; or
    - (iv) any substance to the extent not intended for human consumption before such an exemption takes effect with respect to that substance.

If the compounds are already able to be controlled by the DEA under the Federal Analogue Act and are illegal for recreational use under that act, then there is no reason for the DEA to make the move to place these items in schedule 1 in order to have police powers over them.

Risk of Scheduling

However, the move to schedule 1 WILL make it more complicated for scientists, doctors, researchers and companies to study psychedelics in order to find new treatments for mental health or other diseases and conditions. DOI and DOC are widely used in thousands of medical studies every year due to their lack of scheduling. If this scheduling effort passes researchers across the US will suffer and medical development will suffer and further business will relocate into other countries rather than the United States.
This is due to the fact that schedule 1 compounds are considered as having no medical potential and then require additional licenses which cost additional fees to the DEA, FDA etc in order to research something which is essentially unregulated as a medical product to study now. As such the proposed move to schedule 1 is in antithesis to the fact that these compounds specifically and broadly (~~5ht2a~~) are being shown to have medical use via their 5ht2a activity. LSD, mescaline, DMT and other 5ht2a agonists which are structurally and receptor profile similar are in active trials for medical use. As such there is adequate evidence that these compounds do in fact have medical use and should not be moved to schedule 1.

Currently the DEA, White House and congress are working on and supporting a bill to reduce the restrictions on researching scheduled compounds for medical use. The bill is entitled Halt All Lethal Trafficking of (HALT) Fentanyl Act, which has these policy changes added. The Drug Enforcement Administration (DEA) and National Institute On Drug Abuse (NIDA) say they are in favor of a White House proposal to streamline the process of researching Schedule I drugs like marijuana and certain psychedelics.The agencies testified at a House Energy and Commerce subcommittee hearing recently, expressing support for the Office of National Drug Control Policy (ONDCP) research plan. -
https://www.marijuanamoment.net/bidens-drug-czar-wants-to-make-it-easier-to-research-marijuana-psychedelics-and-other-schedule-i-substances/

Placing these items into schedule 1 seems to be antithesis to the DEA policy move to reduce restrictions for research.

Conclusion

Panacea Plant Sciences as such would like to ask the DEA and federal agencies not to move these items into schedule 1 for the above cited reasons. Regarding the treaty needs to schedule the drugs, we believe that the US is held bound first to US law and then to international treaty. Due to the fact that these items have medical uses they cannot be scheduled under US law. As such the treaty needs should be held subordinate and these items should not be controlled or scheduled further.

Also as states across the country begin to legalize cannabis and psychedelics and hemp is legalized nationally, it begins to look as though the DEA is simply attempting to assert control over new substances in order to stay relevant and secure more funding which is being lost as legalization efforts occur.

Additionally we would like to request a public hearing on these issues and the scheduling. As such in addition to serving as public comment on Docket No. DEA-824, we would also like these comments and statements of fact and request for a hearing shared with and a copy of this statement has been mailed to:

(1)Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (3) Drug Enforcement Administration, Attn: DEA FR Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

David Heldreth
CEO
Panacea Plant Sciences
davidh@panaceaplantsciences.net
www.panaceaplantsciences.net

Attachment B

May 6, 2022
Drug Enforcement Administration, Attn: Hearing Clerk/OALJ

Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, VA 22152.
Subject: Notice of Appearance

Dear Sir:
Please take notice that: ***Daniel J. Lustberg, Elijah Z. Ullman, and Lindsey Galbo*** **will appear in the matter of Schedules of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I,** ***Docket No. DEA824***

(A) (State with particularity the interest of the person in the proceeding.).

See the attached document

(B) (State with particularity the objections or issues, if any, concerning which the person desires to be heard.).

See the attached document

(C) (State briefly the position of the person with regard to the particular objections or issues.).
All notices to be sent pursuant to this appearance should be addressed to:

See the attached document

Respectfully yours,
Elijah Z. Ullman
1063 Burton Drive NE
Atlanta, GA, 30329

On the proposed Schedule 1 classification of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC)

Docket No. DEA824

Executive Summary

Psychedelic drugs such as psilocybin have enjoyed a marked increase in media and scientific attention within the last decade for potential treatment of psychiatric disorders such as post-traumatic stress disorder (PTSD), anxiety, obsessive-compulsive disorder (OCD), and treatment-resistant depression (Tullis, 2021; Sanders, 2021; Vargas et al., 2021). DOI and DOC have proved to be *critical* tools for investigating the function and behavioural pharmacology of the $5HT2_A$ serotonin receptor. Activity at this receptor is thought to be the primary mechanism underlying subjective psychedelic drug effects as well as therapeutic benefit in clinical studies of psychiatric disease (Ling et al., 2021). DOI and DOC have extraordinarily high selectivity for the 5HT2A receptor (Pigott et al., 2012), and produce behavioural effects in animal models that demonstrate face and predictive validity for both psychedelic and therapeutic activity in humans. Importantly, psychedelics are among the least harmful and least likely to be abused of all recreational drugs (Nutt et al., 2010. Indeed, their low abuse potential paired with their clear medical benefits in clinical trials calls into question the legitimacy of their current Schedule 1 status (Nutt et al., 2020). Between 2015 and 2019, DOC was associated with only *three* fatal complications, and *zero* involving DOI (Drug Enforcement Agency, 2022). These numbers pale in comparison to lives claimed by opioids, which are typically Schedule 2 compounds that killed 47,000 Americans by overdose in 2018 alone (Chandler et al., 2020).

Due to its relative ease of accessibility and exceptional pharmacological profile, scientists have gravitated towards DOI and DOC as benchmark compounds in psychopharmacotherapy research. The proposed Schedule 1 classification of DOI and DOC significantly reduces their accessibility as research chemicals for basic science research, essential for drug development and understanding the neurobiology of psychiatric diseases. While laboratories may apply for a Schedule 1 DEA Licence, the proposed legislation will inevitably cause a slowdown in research throughput due to the volume of paperwork and red tape required for a laboratory to apply for a Schedule 1 Licence. Further, many laboratories may simply choose not to apply for a Schedule 1 Licence, and abandon projects within this sector. Thus, the proposed reclassification of DOI and DOC will significantly hamper and deter research underlying treatment resistant-depression and end of life anxiety, and delay the development of future pharmacotherapeutics for treating these disorders. All of this promising research relies on complete characterization of $5HT2_A$ function.

Context

Activation of the 5HT2A receptor is a common mechanism of action for all serotonergic psychedelic drugs and is likely necessary for their profound emotional, cognitive, and sensory effects, as well as their therapeutic effects. DOI was synthesised by the pioneering biochemist Alexander Shulgin, who was himself a consultant and researcher for the DEA (Nutt et al., 2020).

Because commonly used psychedelics like psilocybin and LSD had been classified as Schedule I drugs in 1970, DOI and DOC have represented legal and accessible research chemical alternatives to working with traditional psychedelics that had been widely used for "psycholytic therapy" in the 1960s. Since 2012, DOI has been utilised in approximately 1,200 research articles in leading journals such as Cell, Nature, and Science (Tullis, 2021). After psychedelics such as LSD and psilocybin were classified as Schedule 1, psychiatric studies on these interesting compounds with all of their promising results ground almost completely to a halt for several decades (Nutt et al., 2020). The profound effects of psilocybin on end-of-life anxiety and treatment-resistant depression have been extensively reported upon in the scientific literature (Griffiths et al., 2016. Tullis, 2021, Davis et al., 2020). The process to obtain a Schedule 1 licence is long, arduous, and burdensome for many laboratories that want to work with such substances. Due to DOI and DOC's potential medical value and relative lack of abuse, it does not follow scientific or logical reasoning to place it into Schedule 1 category. Psychedelics are among the least harmful and least likely to be abused of all recreational drugs (Nutt et al., 2010; Nutt et al., 2020), and it is morally wrong to impede the efforts of scientists working to develop therapeutics that could prevent suicide, eliminate PSTD in combat veterans, break the cycle of drug addiction, and alleviate intrusive thoughts and compulsive symptoms in patients with conditions that do not respond to currently available drugs like typical antidepressants (Sellers & Leiderman, 2018).

The DEA should not move to reclassify DOI and DOC as Schedule 1 compounds. As we know, this practice promotes the development of untested analogues that may be more dangerous than the compounds they mimic. The cycle of designing analogues to bypass DEA regulations is a well-established phenomenon (Koh et al., 2018), and reclassifying DOI and DOC will lead down the same road. The synthetic cannabinoid, AM-2201, became more prevalent following the DEA's scheduling of cannabinoid JWH-018. The two compounds are nearly identical, yet small changes can circumvent the DEA's scheduling (Crews, 2013). The chemical changes may lead to unexpected metabolic products which are more harmful to the consumer than the well-established safety profile of Δ^9-THC. The truth is, psychedelics like psilocybin are coming down the FDA regulatory pipeline whether the FDA or DEA likes it or not, and these drugs will soon enter the consumer marketplace (**Fig. 1**). This resurgence in interest in

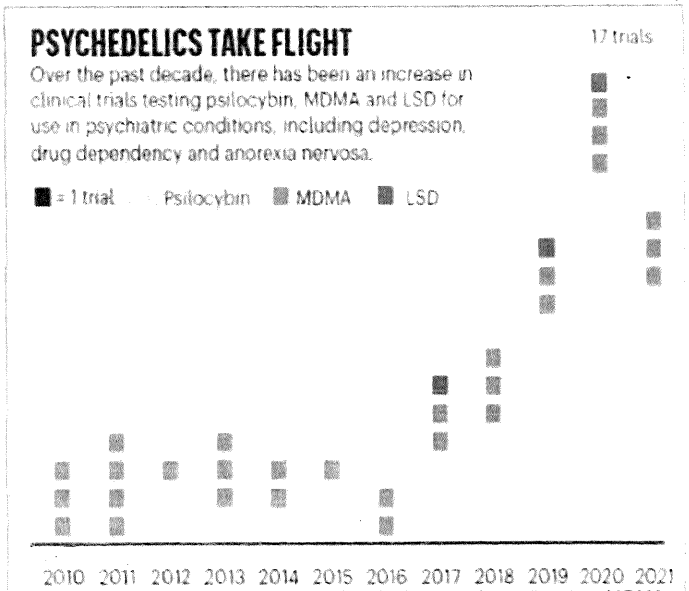

Figure 1; Funding for and execution of clinical trials using psilocybin, MDMA, and LSD for psychiatric research in humans have steadily increased over the last decade, peaking in 2020. Tullis, 2021. *How ecstasy and psilocybin are shaking up psychiatry. Nature, 589*(7843), 506-510.

psychedelic therapy is in no small part due to the data generated from basic science research using DOI and DOC to elucidate $5HT2_A$ receptor pharmacology and actions on synaptic plasticity (**Fig. 2**). It is of interest to all parties involved that we achieve a scientific understanding of the mechanism of action of these compounds, which will be widely used in psychiatric settings within a matter of years (Nutt & Carhart-Harris, 2021).

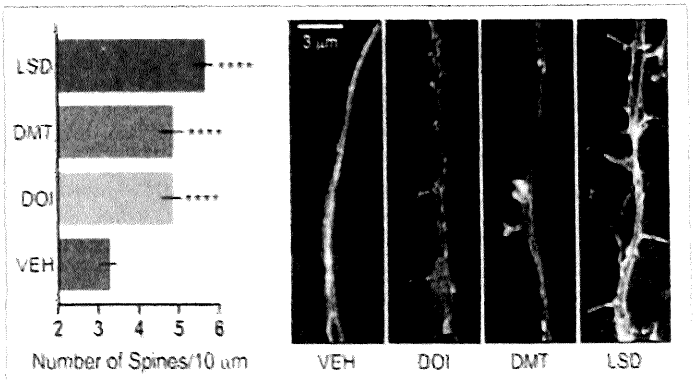

Figure 2: DOI and classic psychedelics like DMT and LSD swiftly promote the growth of dendritic spines, possibly acting as plastinogens to exert their rapid therapeutic effects in animal models of psychiatric disease. (Ly et al., 2018 Psychedelics promote structural and functional neural plasticity. Cell reports, 23(11), 3170-3182.

Recommendations

1) Maintain DOI and DOC current non-scheduled status to expedite research into the $5HT2_A$ Receptor, and promote development of future pharmacotherapeutics inspired by this work.

2) Establish a new framework to remove Schedule 1 DEA licensing requirements for any laboratories with a Schedule II licence, allowing them to study Schedule 1 substances. In the context of DOI and DOC, the DEA's own position is that the drugs do not appear "on the streets" via illegal dispersal from scientific research laboratories (Drug Enforcement Agency, 2022), so this modest allowance is unlikely to increase the amount of illegally trafficked DOI/DOC.

Daniel J. Lustberg, PhD (Molecular and Systems Pharmacology, Emory University); currently using DOI for preclinical studies on animal models of OCD and PTSD. Primary expertise in neuroanatomy, neural circuits, neuromodulatory systems, behavioural pharmacology, cell signalling, drug development, toxicology, and human clinical research. He is also an advocate for sensible drug policy in the US, as well as compassionate use of psychedelics and other related experimental compounds as pharmacotherapies for treatment-resistant psychiatric disorders.

Lindsey Galbo, PhD Candidate (Integrative Physiology and Pharmacology, Wake Forest University); 2020-2021 American Society for Pharmacology and Experimental Therapeutics (ASPET) Policy Fellow, Co-Chair of the Scientific Policy Council for Students for Sensible Drug Policy. Founding President of Students for Sensible Drug Policy at Wake Forest School of Medicine. Lindsey currently studies the behavioural pharmacology of alcohol and cocaine, and investigating novel pharmacotherapies for treating alcohol abuse.

Elijah Z. Ullman, PhD Candidate (Molecular and Systems Pharmacology, Emory University), Co-Chair of the Scientific Policy Council for Students for Sensible Drug Policy. Founding President of Students for Sensible Drug Policy at Colorado State University. Elijah currently studies the

molecular pharmacology underlying conductance-modification of the NMDA Receptor and dynamics of the ion channel pore.

Citations:

- Chandler, R. K., Villani, J., Clarke, T., McCance-Katz, E. F., & Volkow, N. D. (2020). Addressing opioid overdose deaths: The vision for the HEALing communities study. *Drug and Alcohol Dependence*, *217*, 10832
- Crews, B. (2013, February 1). *Synthetic cannabinoids*. Synthetic Cannabinoids The Challenges of Testing for Designer Drugs. Retrieved May 5, 2022, from https://www.aacc.org/cln/articles/2013/february/cannabinoids
- Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2020). Effects of psilocybin-assisted therapy on major depressive disorder. *JAMA Psychiatry*, *78*(5), 481. https://doi.org/10.1001/jamapsychiatry.2020.3285
- Drug Enforcement Agency. (2022, April 11). *Schedules of controlled substances: Placement of 2,5-dimethoxy-4 ...* Federal Register. Retrieved May 3, 2022, from https://www.federalregister.gov/documents/2022/04/11/2022-07648/schedules-of-controlled-substances-placement-of-25-dimethoxy-4-iodoamphetamine-doi-and
- Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, *30*(12), 1181–1197. https://doi.org/10.1177/0269881116675513
- Koh, H. K., Kerlikowske, R. G., & Botticelli, M. P. (2018). A smarter war on drugs. *JAMA*, *320*(22), 2301-2302.
- Ling, S., Ceban, F., Lui, L. M., Lee, Y., Teopiz, K. M., Rodrigues, N. B., ... & McIntyre, R. S. (2021). Molecular Mechanisms of Psilocybin and Implications for the Treatment of Depression. *CNS drugs*, 1-14.
- Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Soltanzadeh Zarandi, S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics promote structural and functional neural plasticity. *Cell Reports*, *23*(11), 3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022
- Nutt, D. J., King, L. A., & Phillips, L. D. (2010). Drug harms in the UK: A multicriteria decision analysis. *The Lancet*, *376*(9752), 1558–1565. https://doi.org/10.1016/s0140-6736(10)61462-6
- Nutt, D., Erritzoe, D., & Carhart-Harris, R. (2020). Psychedelic psychiatry's brave new world. *Cell*, *181*(1), 24-28.
- Nutt, D., & Carhart-Harris, R. (2021). The current status of psychedelics in psychiatry. *JAMA psychiatry*, *78*(2), 121-122.
- Pigott, A., Frescas, S., McCorvy, J. D., Huang, X.-P., Roth, B. L., & Nichols, D. E. (2012). trans-2-(2,5-dimethoxy-4-iodophenyl)cyclopropylamine and trans-2-(2,5-dimethoxy-4-bromophenyl)cyclopropylamine as potent agonists for the 5-HT2 receptor family. *Beilstein Journal of Organic Chemistry*, *8*, 1705–1709. https://doi.org/10.3762/bjoc.8.194
- Sanders, L. (2021, December 3). *Can psychedelics meet their potential for treating mental health disorders?* Science News. Retrieved May 3, 2022, from https://www.sciencenews.org/article/psychedelic-drugs-treatment-mental-health-disorders-depression
- Sellers, E. M., & Leiderman, D. B. (2018). Psychedelic drugs as therapeutics: No illusions about the challenges. *Clinical Pharmacology & Therapeutics*, *103*(4), 561-564.
- Tullis, P. (2021, January 27). *How ecstasy and psilocybin are shaking up psychiatry*. Nature News. Retrieved May 3, 2022, from https://www.nature.com/articles/d41586-021-00187-2
- Vargas, M. V., Meyer, R., Avanes, A. A., Rus, M., & Olson, D. E. (2021). Psychedelics and other psychoplastogens for treating mental illness. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.727117