For the Purpose of § 1316.47 *Request for Hearing Regarding Docket No.1156*

On behalf of the Science Policy Council, Students for Sensible Drug Policy
C/O Elijah Zorro Ullman

Docket No. DEA1156

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

The below signatories are interested persons in the Request for Hearing on DEA1156, and have standing for a hearing on this matter as they are scientists utilising or have utilised DOI in their research.

Executive Summary

Psychedelic drugs such as psilocybin have experienced 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), treatment-resistant depression and substance use disorders (Bogenschutz et al., 2022; Johnson et al., 2017; Sanders, 2021; Tullis, 2021; Vargas et al., 2021). Yet, many of these psychedelics act through a wide variety of receptor systems, and the exact identity, localization, and downstream mechanisms of the molecular targets that account for their therapeutic efficacy is an active area of research. DOI and DOC are invaluable research tools to study these receptor systems and their roles in therapeutic effects because, unlike more conventional psychedelic drugs such as psilocybin, DOI and DOC are highly selective for serotonin 2 receptors (5-HT_2). Activity at these receptors is thought to be the primary mechanism underlying subjective psychedelic drug effects as well as therapeutic benefit in clinical studies of psychiatric disease (Jaster & González-Maeso, 2023; Ling et al., 2022). Importantly, psychedelics are among the least harmful and least likely to be abused of all recreational drugs, considering their sporadic use patterns, non-reinforcing effects and rapid tolerance to the hallucinations and subjective effects (de la Fuente Revenga et al., 2022; Fantegrossi et al., 2004). 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). The undersigned therefore asks for no changes in the scheduling of DOI and DOC due to their importance in serotonin and psychedelic pharmacology. We also Request a Hearing on this matter pursuant to 21 CFR 1316.47 as *Interested Persons.* Placement of DOI and DOC in Schedule 1 of the CSA is not commensurate with its abuse potential, and is further complicated by its extensive utility in scientific research as detailed below.

Interest of Petitioners

Placement of DOI and DOC in Schedule 1 of the CSA will cause irreparable harm to the research endeavours of the Undersigned; Placement in Schedule 1 will prevent the Undersigned from conducting their research. The Undersigned have significant expertise in behavioural and molecular models of addiction and characterization of the ensuing biochemistry and pharmacology. See the below Biographies for further information.

Actual or Relative Abuse Potential

Psychedelics have long been characterised for their unusual effects on sensory perception and subjective experiences. Until the last ten years, psychedelics have not been fully investigated utilising modern methodology or institutional review board regulations for their own use liability or ability to reduce drug use in both clinical and preclinical models.

While the Controlled Substances Act uses drug discrimination as an *in vivo* test to assess drug use liability in comparison to known “drugs of abuse”, the core of drug discrimination is to evaluate the stimulus similarity between a test novel chemical entity and a reference agent. While psychedelics like DOI and DOC do substitute for DOM, LSD and psilocybin, this is due to their shared pharmacology at the 5-HT_2 receptors

(Glennon et al., 1982). As DOI and DOC's duration is approximately 36 hours in humans, the potential for abuse is minimal, as exemplified by relative lack of seizures of the compounds by law enforcement. In recent years, other measures that are more widely accepted tests of drug use include self-administration, intracranial self-stimulation and food versus drug choice operant responding (Spanagel, 2017). *In these more rigorous measures, DOI and some analogs have been shown to be non-reinforcing and to reduce reinforcing effects of other drugs*. Due to their long duration of action of 24+ h, much longer than other serotonergic psychedelics like LSD, they are less likely to be abused - as evidenced by the statistics). Law enforcement seizures have been exceptionally minimal (Drug Enforcement Administration, 2023b). It follows that compounds that are non-reinforcing, are generally non-addictive.

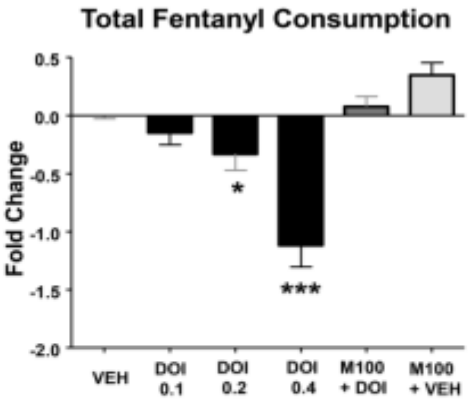

Figure 1. Decrease in fentanyl consumption shown as Log2 fold-change for each drug condition relative to the log-average of all vehicle sessions. Martin, 2021. Effects of 5-HT2A Receptor Stimulation on Economic Demand for Fentanyl after Intermittent and Continuous Access Self-Administration in Male Rats. *Addiction Biology*, 2021;26(3).

For example, DOM decreased heroin self-administration in non-human primates but did not alter food responding (Maguire, 2023). Similarly, DOI depressed intracranial self-stimulation in rats, which is in contrast to other drugs like heroin, cocaine and amphetamines, which typically stimulate responding (Jaster et al., 2022), and DOI was found to decrease ethanol preference in a conditioned place preference and two-bottle choice model (Oppong-Damoah et al., 2019). Most profoundly, DOI was found to dose-dependently decrease motivation for fentanyl seeking and decrease low-cost and total fentanyl consumption, which was evidenced to be dependent on 5-HT_{2A} activation (**Fig. 1** taken from (Martin et al., 2021). DOI was also found to accelerate natural extinction of opioid preference using a mouse conditioned place preference model (Jaster et al., 2024, unpublished).

To this end, if the same logic is applied to drug discrimination, all of these compounds may produce non-reinforcing effects and potentially attenuate use of other substances and therefore do not fall into the "high potential for abuse" category. With this consideration, the proposed reclassification of DOI and DOC into Schedule I of the CSA would be inappropriate solely based on the lack of indication for "high potential for abuse" and no "medicinal value," as there is a growing body of evidence that contradicts this opinion.

Importance as a Scientific Tool and Impact of Schedule 1 Classification

Because commonly used psychedelics like psilocybin and LSD had been classified as Schedule 1 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.

DOI in particular, and phenethylamines like DOC in general, are extremely useful compounds for scientific research because they are highly selective agonists for 5-HT receptors over other closely related G-protein coupled receptors (Halberstadt et al., 2009, 2013). Specifically, DOI is especially important as a research chemical due to its high selectivity for the 5-HT_2 class of 5-HT receptors, including the 5-HT_{2A} receptor, which is known to be critical for the therapeutic effects of psychedelics (Cameron et al., 2021). As polypharmacology — the affinity of a compound for multiple receptors — complicates scientific study of the receptor of interest, the availability of DOI and related phenethylamines for scientific research is paramount.

Since 2012, DOI has been utilised in approximately 1,200 research articles in leading journals such as Cell, Nature, and Science. This number has only grown in the last two years. Scientists have gravitated towards DOI and DOC as benchmark compounds in pharmacotherapy research for diseases of the central and peripheral nervous systems due to its relative ease of accessibility and exceptional pharmacological profile. For example, a significant research effort has been undertaken to understand the crucial role of serotonin in the neuro-immune interactions that govern pain (Loyd et al., 2013; Richardson, 1990). In order to understand the role of the 5-HT_{2A} receptor in neuropathic pain, DOI has been used for behavioural, electrophysiological, cellular, and molecular experiments (Abbott et al., 1996; Kjørsvik Bertelsen et al., 2003; Rahman et al., 2011; Tokunaga et al., 1998). Further, DOI and its phenylethylamine analogs are being studied for chronic pain and as anti-inflammatory agents (Nichols, 2022), making them an important tool to understand and develop better and less addictive pain medications than opioids. Most recently, $1.5 million was granted by the Howard Hughes Medical Institute in 2023 to specifically study the effects of DOI on peripheral pain neurons.

The proposed Schedule 1 classification of DOI and DOC significantly reduces their accessibility as research chemicals for basic science research which is essential for novel drug development and understanding of conditions like pain, substance use and neuropsychiatric diseases. While laboratories may apply for a Schedule 1 DEA Licence, it is well understood amongst the scientific community that the financial barriers and bureaucratic red tape associated with obtaining a Schedule 1 licence and conducting research with these compounds amounts to a nearly prohibitive roadblock for many laboratories (Andreae et al., 2016; Henningfield et al., 2022). As such, many laboratories - including many of the Undersigned - 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 medical research, and delay the development of future pharmacotherapeutics for treating a variety of neuropsychiatric, substance use and inflammatory disorders. All of this promising research relies on complete characterization of the function of 5-HT_2 receptors.

Danger to Self and Public Health

According to the DEA, in the 19 years since these two compounds were first encountered by law enforcement in the U.S. there have only been *three* fatal complications associated with the use of DOC and *zero* involving DOI (Drug Enforcement Administration, 2023a). 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). In one case report in which DOC was attributed to death included the use of other compounds - the presence of DOC was negligible (< 10 ng/mL in cardiac blood sample) - but buprenorphine, cocaine and cannabis metabolites were also present complicating the cause of death (Lelievre et al., 2022).

There is ample scientific literature describing the fact that, on their own, many psychedelics have no known lethal dose and have minimal physiological toxicity. For commonly-used psychedelics like psilocybin and LSD, only a handful of overdose cases not involving other drugs have been documented, and their lethal doses have been estimated to be at least *one-thousand times* a standard dose (Gable, 2004). Other known physiological side effects of psychedelics, including acute autonomic effects, pulse and breathing irregularities, and headaches are relatively mild and often do not pose major health risks to the individual (Johnson et al., 2018). Although less is known about the possible toxicity associated with DOI and DOC, it is reasonable to assume they share similar properties as more commonly-used psychedelics like psilocybin and LSD, as they share similar pharmacological profiles. It is therefore, in our opinion, safe to assume that there is little concern for physiological toxicity or lethal outcomes with DOI and DOC.

Conclusion

Activation of the 5-HT_2 receptors 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. The significant effects of psychedelics on end-of-life anxiety, treatment-resistant depression, and substance use disorders have been extensively reported upon in the scientific literature in both humans and preclinical models (Davis et al., 2021; Griffiths et al., 2016; Jaster & González-Maeso, 2023; Tullis, 2021). See **Fig. 2** taken from Tullis et al., 2021.

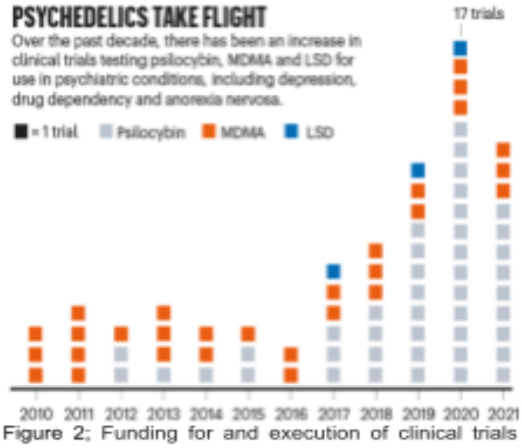

Figure 2; Funding for and execution of clinical trials using psilocybin, MDMA, and LSD for psychiatric research in humans have steadily increased over the last decade, peaking in 2020. Tullis, 2021. How ecstasy and psilocybin are shaking up psychiatry. *Nature*, 589(7843), 506-510.

Research using DOI and DOC is ongoing in a variety of fields that have a large impact on health. Both published and unpublished work with DOI has demonstrated its own potential utility in treatment of substance use disorders, including alcohol and opioid use (Oppong-Damoah et al., 2019; Jaster et al., 2024, unpublished). Restriction of access to these compounds within the research setting will hamper the ability to further study the utility of DOI and other psychedelics for these indications.

The process to obtain a Schedule 1 licence is long, arduous, and burdensome for laboratories that want to work with such substances. Due to DOI and DOC's value to scientific research and relative lack of abuse, it does not follow scientific or logical reasoning to place it into the Schedule 1 category. It is our opinion that 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 (Sellers & Leiderman, 2018).

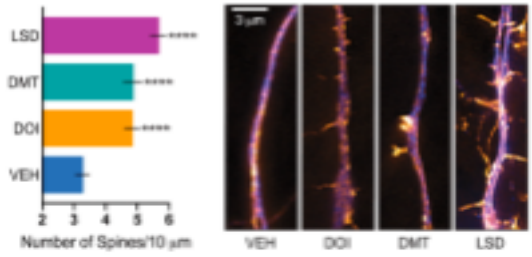

Figure 3; DOI and classic psychedelics like DMT and LSD swiftly promote the growth of dendritic spines, possibly acting as plastinogens to exert their rapid therapeutic effects in animal models of psychiatric disease.. Ly et al., 2018. Psychedelics promote structural and functional neural plasticity. Cell reports, 23(11), 3170-3182.

Lastly, classical and non-classical psychedelics like psilocybin and MDMA respectively, are coming down the FDA regulatory pipeline and these drugs will soon enter the consumer marketplace (Center for Drug Evaluation and Research, 2023; MAPS PBC, 2023). This resurgence in interest in psychedelic therapy is in no small part due to the data generated from basic science research using phenethylamines such as DOI to elucidate 5HT_2 receptor pharmacology and actions on structural and synaptic plasticity (de la Fuente Revenga et al., 2021; Desouza et al., 2021; Ly et al., 2018). See **Fig. 3** taken from Ly et al. 2018.

It is of interest to all parties involved that we achieve a scientific understanding of the mechanisms of action of these compounds, which will be widely used in psychiatric settings within a matter of years (Nutt & Carhart-Harris, 2021).

Recommendations

1) Maintain the current non-scheduled status of DOI and DOC to expedite research into 5-HT_2 receptors and their influence on disease states and chronic pain.

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. Restrictions on researching Schedule 1 substances places undue and strenuous burden on researchers, an opinion shared by Dr. Nora Volkow, the Director of the National Institutes of Drug Abuse, and others in the research community (*Statement of Nora Volkow, M.D. Hearing on Cannabis Policies for the Next Decade*, 2020). In the context of DOI and DOC, the DEA's own position is that these drugs do not appear "on the streets" via illegal dispersal from scientific research laboratories (Drug Enforcement Administration, 2023a), so this modest allowance is unlikely to increase the amount of illegally trafficked DOI and DOC.

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