ASPET
Transforming Discoveries into Therapies

January 12, 2024

Drug Enforcement Administration
Attn: DEA FR Representative/DPW
8701 Morrissette Drive
Springfield, Virginia 22152

RE: Schedules of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I (DEA-2023-0168)

Submitted electronically via regulations.gov.

The American Society for Pharmacology and Experimental Therapeutics (ASPET) appreciates the opportunity to provide comments on the Request for Information regarding flexibilities for streamlining protocol review. ASPET is a 4,000-member scientific society whose members conduct basic and clinical pharmacological research and work in academia, government, industry, and non-profit organizations. ASPET members conduct research leading to the development of new medicines and therapeutic agents to fight existing and emerging diseases.

ASPET urges and recommends that the DEA schedule neither DOI nor DOC under Docket No. DEA1156 in the Controlled Substances Act (CSA). DOI and DOC do not have “high potential for abuse” and are used extensively for research in the scientific community. ASPET feels that the inclusion of DOI and DOC on the Schedule I will create unintended administrative burden and chill scientific research and discovery.

1. Actual or Relative Potential for Abuse:
While DOI and DOC substitute for DOM, LSD, and psilocybin in some assayssuggesting hallucinogenic-like effects, this pattern is not reflected in human usage as supported by exceptionally low drug seizures by law enforcement.[1] In the past 20 years, there have been only three fatalities associated with DOC and none with DO1.[23] In 2018 for comparison, 47,000 Americans died from opioid overdose alone.[4]

2. Scientific evidence of its pharmacological effects, if known:
Indeed, there is no FDA-approved medical use for DOI. However, DOI specifically is an exceptionally useful tool to investigate 5HT2 receptor pharmacology, due to its high specificity over other subunits or receptors.[56] In the last decade, DOI has been cited in more than 1,200 papers, indicating high utility in literature. In intracranial self-stimulation models, DOI has been demonstrated to be non-reinforcing, and reduce fentanyl administration as well.[7] Given the emerging evidence, it seems inappropriate to limit scientific research through placement of DOI in Schedule 1. Many researchers indicate Schedule 1 prohibits research endeavors significantly. [8]

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[1] Glennon, R. A., Young, R., Benington, F., & Morin, R. D. (1982). Behavioral and serotonin receptor properties of 4-substituted derivatives of the hallucinogen 1-(2,5-dimethoxyphenyl)-2-aminopropane. Journal of Medicinal Chemistry, 25(10), 1163–1168. https://doi.org/10.1021/jm00352a013

[2] Drug Enforcement Administration. (2023). DEA1156 Eight-Factor Review DOI DOC 102023 (DEA-2023-0168-0005). https://www.regulations.gov/document/DEA-2023-0168-0005

[3] Expert Committee on Drug Dependence. (2019). 42nd ECDD (2019) Critical Review: DOC (4-Chloro-2,5-dimethoxyamfetamine (Forty-Second Meeting). World Health Organization. https://researchonline.ljmu.ac.uk/id/eprint/11444/1/ECDD42_DOC.pdf

[4] 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, 108329. https://doi.org/10.1016/j.drugalcdep.2020.108329

[5] Halberstadt, A. L., Powell, S. B., & Geyer, M. A. (2013). Role of the 5-HT2A receptor in the locomotor hyperactivity produced by phenylalkylamine hallucinogens in mice. Neuropharmacology, 70, 218–227. https://doi.org/10.1016/j.neuropharm.2013.01.014

[6] Halberstadt, A. L., van der Heijden, I., Ruderman, M. A., Risbrough, V. B., Gingrich, J. A., Geyer, M. A., & Powell, S. B. (2009). 5-HT2A and 5-HT2C receptors exert opposing effects on locomotor activity in mice. Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, 34(8), 1958–1967. https://doi.org/10.1038/npp.2009.29

[7] Martin, D. A., Gyawali, U., & Calu, D. J. (2021). Effects of 5-HT2A receptor stimulation on economic demand for fentanyl after intermittent and continuous access self-administration in male rats. Addiction Biology, 26(3), e12926. https://doi.org/10.1111/adb.12926

[8] See: Further information on DOI pharmacology: Jaster, A. M., & González-Maeso, J. (2023). Mechanisms and molecular targets surrounding the potential therapeutic effects of psychedelics. Molecular Psychiatry, 28(9), Article 9. https://doi.org/10.1038/s41380-023-02274-x

3. The state of current scientific knowledge regarding the drug or other substances:
The analysis shows the chemical makeup and confirms the fact that DOI and DOC are hallucinogenic. Typically, LD50s for a psychedelic is 1,000x greater than its pharmacological dose, a therapeutic window significantly wider than that known for opiates or amphetamines.[9]

4. Its history and current pattern of abuse:
Three overdose deaths in a 20 year period for DOC, and none for DOI is indicative of its relative lack of lethality. [10] Law enforcement seizures in the last twenty years have been minimal.

5. The scope, duration, and significance of abuse:
DOC and DOI each have a long 36-hour duration-of-action that undermines their reinforcing effects and abuse liability. If otherwise, law enforcement seizures would be greater and reflective of the high abuse of these drugs – law enforcement officers still seize illicit opiates, amphetamines, and psychedelics. Careful consideration should be given to rigorously and scientifically evaluate the abuse potential of these drugs before placing them under Schedule I based on their perceived "abuse" potential.

6. What, if any, risk there is to the public health:
As previously stated, opiate-related deaths in 2018 were approximately 47,000 and in a 20 year period, there have been zero DOI-related deaths, and three DOC-related deaths.[11] Pharmacological and psychoactive effects of psychedelics generally include acute autonomic effects, pulse and breathing irregularities (though not lethal), and headache. However, these are relatively mild, and largely do not pose major health risks.[12] Psilocybin, another psychedelic with similar pharmacology to DOI and DOC, has demonstrated reduction in alcohol consumption in a

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[9] See: Further information on scientific knowledge: Jaster, A. M., & González-Maeso, J. (2023). Mechanisms and molecular targets surrounding the potential therapeutic effects of psychedelics. Molecular Psychiatry, 28(9), Article 9. https://doi.org/10.1038/s41380-023-02274-x
Johnson, M. W., Griffiths, R. R., Hendricks, P. S., & Henningfield, J. E. (2018). The Abuse Potential of Medical Psilocybin According to the 8 Factors of the Controlled Substances Act. Neuropharmacology, 142, 143–166. https://doi.org/10.1016/j.neuropharm.2018.05.012
Nutt, D., & Carhart-Harris, R. (2021). The Current Status of Psychedelics in Psychiatry. JAMA Psychiatry, 78(2), 121–122. https://doi.org/10.1001/jamapsychiatry.2020.2171
Sellers, E. M., & Leiderman, D. B. (2018). Psychedelic Drugs as Therapeutics: No Illusions About the Challenges. Clinical Pharmacology and Therapeutics, 103(4), 561–564. https://doi.org/10.1002/cpt.776

[10] Drug Enforcement Administration. (2023). DEA1156 Eight-Factor Review DOI DOC 102023 (DEA-2023-0168-0005). https://www.regulations.gov/document/DEA-2023-0168-0005
Henningfield, J. E., Coe, M. A., Griffiths, R. R., Belouin, S. J., Berger, A., Coker, A. R., Comer, S. D., Heal, D. J., Hendricks, P. S., Nichols, C. D., Sapienza, F., Vocci, F. J., & Zia, F. Z. (2022). Psychedelic drug abuse potential assessment research for new drug applications and Controlled Substances Act scheduling. Neuropharmacology, 218, 109220. https://doi.org/10.1016/j.neuropharm.2022.109220
Lelievre, B., Dupont, V., Buchaillet, C., Jousset, N., Deguigne, M., & Cirimele, V. (2022). Difficulties interpreting concentrations in fatal cases: Example of 2,5-dimethoxy-4-chloroamphetamine. Forensic Toxicology, 40(2), 383–392. https://doi.org/10.1007/s11419-022-00628-8

[11] Drug Enforcement Administration. (2023). DEA1156 Eight-Factor Review DOI DOC 102023 (DEA-2023-0168-0005). https://www.regulations.gov/document/DEA-2023-0168-0005

[12] Johnson, M. W., Griffiths, R. R., Hendricks, P. S., & Henningfield, J. E. (2018). The Abuse Potential of Medical Psilocybin According to the 8 Factors of the Controlled Substances Act. Neuropharmacology, 142, 143–166. https://doi.org/10.1016/j.neuropharm.2018.05.012

clinical trial and improvement in depression symptoms in another clinical trial.[13] The implied minimal fatality concerns related to these types of drugs combined with the DEA's assertion that DOC and DOI are not being diverted from legitimate research labs, negate the requirement to place these drugs in Schedule 1 of the CSA.

7. Psychic or physiological dependence liability:
A DOM analog decreased heroin-self administration in non-human primates but did not alter food responding behavior.[14] DOI depresses intracranial self-stimulation in rats which is opposite to other drugs like heroin, cocaine and amphetamines which all stimulate responding.[15] DOI was found to decrease ethanol preference in the conditioned place preference and two-bottle choice models.[16] Further, DOI was found to have dose-dependently decreased motivation for fentanyl seeking and decreased low-cost and total fentanyl consumption, which was evidenced to be dependent on 5-HT2A activation.[17] DOI was found to accelerate natural extinction of opioid preference using a mouse conditioned place preference model.[18] Taken together, this evidence suggests low abuse potential for DOI, and importantly even, pharmacological benefits to mitigating other substance use disorders.

8. Whether the substance is an immediate precursor of a substance already controlled:
Neither DOI or DOC are an immediate precursor of a substance already controlled, and thus this factor is not relevant for these two substances.

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[13] Bogenschutz, M. P., Ross, S., Bhatt, S., Baron, T., Forcehimes, A. A., Laska, E., Mennenga, S. E., O'Donnell, K., Owens, L. T., Podrebarac, S., Rotrosen, J., Tonigan, J. S., & Worth, L. (2022). Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry, 79(10), 953–962. https://doi.org/10.1001/jamapsychiatry.2022.2096
Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry, 78(5), 481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285

[14] Maguire, D. R. (2023). Effects of 2,5-Dimethoxy-4-Methylamphetamine (DOM) and 2-Piperazin-1-yl-Quinoline (Quipazine) on Fentanyl Versus Food Choice in Rhesus Monkeys. The Journal of Pharmacology and Experimental Therapeutics, 384(1), 155–162. https://doi.org/10.1124/jpet.122.001318

[15] Jaster, A. M., Elder, H., Marsh, S. A., de la Fuente Revenga, M., Negus, S. S., & González-Maeso, J. (2022). Effects of the 5-HT2A receptor antagonist volinanserin on head-twitch response and intracranial self-stimulation depression induced by different structural classes of psychedelics in rodents. Psychopharmacology, 239(6), 1665–1677. https://doi.org/10.1007/s00213-022-06092-x

[16] Oppong-Damoah, A., Curry, K. E., Blough, B. E., Rice, K. C., & Murnane, K. S. (2019). Effects of the synthetic psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI) on ethanol consumption and place conditioning in male mice. Psychopharmacology, 236(12), 3567–3578. https://doi.org/10.1007/s00213-019-05328-7

[17] Martin, D. A., Gyawali, U., & Calu, D. J. (2021). Effects of 5-HT2A receptor stimulation on economic demand for fentanyl after intermittent and continuous access self-administration in male rats. Addiction Biology, 26(3), e12926. https://doi.org/10.1111/adb.12926

[18] Jaster, A. M., & González-Maeso, J. (2023). Mechanisms and molecular targets surrounding the potential therapeutic effects of psychedelics. Molecular Psychiatry, 28(9), Article 9. https://doi.org/10.1038/s41380-023-02274-x

Conclusion:

- There is a dearth of evidence for law enforcement seizures of DOI and DOC.
- There is a lack of DOI and DOC overdose-related deaths.
- There is preclinical evidence for DOI reducing the reinforcing properties of drugs of abuse, including ethanol and fentanyl.
- DOI and DOC do not have “high potential for abuse” and are used extensively for research in the scientific community. Many labs may choose to simply abandon projects involving these compounds rather than pursue the hassle of a Schedule 1 license should these be placed in Schedule I.[19]

[19] Henningfield, J. E., Coe, M. A., Griffiths, R. R., Belouin, S. J., Berger, A., Coker, A. R., Comer, S. D., Heal, D. J., Hendricks, P. S., Nichols, C. D., Sapienza, F., Vocci, F. J., & Zia, F. Z. (2022). Psychedelic drug abuse potential assessment research for new drug applications and Controlled Substances Act scheduling. Neuropharmacology, 218, 109220. https://doi.org/10.1016/j.neuropharm.2022.109220
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