U.S. Department of Justice

Drug Enforcement Administration

Schedule of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in schedule I

Background, data, and analysis: Eight factors determinative of control and findings pursuant to 21 U.S.C. 812(b)

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I. Background

Hallucinogens, such as such as lysergic acid diethylamide (LSD), psilocyn, and 2,5-dimethoxy-4-methamphetamine (DOM), are a diverse group of natural and synthetic substances that alter perception, cognition, and mood. The subjective effects of hallucinogens drive their abuse. The abuse of these substances can lead to a variety of adverse health effects, such as paranoia, agitation, depression, and violent outbursts, towards self and others (Carbonaro et al., 2016). Intoxication and deaths associated with the abuse of hallucinogens have been reported.

The Drug Enforcement Administration (DEA) and international bodies continue to monitor law enforcement and public health data pertaining to the trafficking and abuse of hallucinogens, both natural and synthetic substances, which are readily available over the Internet and sold through illicit channels. Their abuse has been associated with both acute and long-term public health and safety problems, including emergency room admissions and deaths. This class of substances is generally encountered in tablet, capsule, or powder forms. Two such hallucinogens are 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC), which are structural analogs of DOM, a schedule I hallucinogen.

DOI and DOC have no known medical use in the United States (U.S.) and are not marketed internationally as approved drug products. Both have been reported as drugs of abuse in the U.S. and internationally by law enforcement authorities and identified in seizures. In response to reports of abuse and trafficking, DEA gathered the available information regarding the pharmacology, chemistry, trafficking, actual abuse, pattern of abuse, and the relative potential for abuse and dependence of these hallucinogens. On September 26, 2018, pursuant to 21 U.S.C. 811(b) of the Controlled Substances Act (CSA), DEA sent this data review document to the Assistant Secretary for Health of the Department of Health and Human Services (HHS)[1] with a request to provide scientific and medical evaluations and scheduling recommendations for DOI and DOC. On May 7, 2020, the Secretary General of the United Nations advised the Secretary of State of the U.S. that the United Nations Commission on Narcotic Drugs (UN/CND), at its 63rd session held on March 4, 2020, voted to place DOC in Schedule I of the 1971 Convention on Psychotropic Substances (1971 Convention) in accordance with the evaluation and recommendation from the World Health Organization (WHO). The U.S. is a signatory to the 1971 Convention. As a signatory to this international treaty, the United States is required, by scheduling under the Controlled Substances Act (CSA), to place appropriate controls on DOC to meet the requirements of the treaty.

[1] As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of HHS has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

On September 28, 2020, HHS provided to DEA scientific and medical evaluation and scheduling recommendation DOI and DOC. The scientific and medical evaluation was entitled: "Basis for the Recommendation to Control 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) and their Salts in Schedule I of the Controlled Substances Act (CSA)" (HHS, 2020). Following consideration of the eight factors and findings related to the substance's abuse potential, legitimate medical use, and dependence liability, the HHS recommended that DOI and DOC be controlled in schedule I of the CSA under 21 U.S.C. § 812(b).

The CSA requires the Administrator of DEA, as delegated by the Attorney General,[2] to determine whether HHS's scientific and medical evaluation, scheduling recommendation, and all other relevant data constitute substantial evidence that a substance should be scheduled. 21 U.S.C. 811(b). This document contains an explanation of DEA's determination to place DOI and DOC in schedule I of the CSA.

II. Eight Factors Determinative of Control

Pursuant to 21 U.S.C. 811(c), DEA must consider eight factors in making any findings of substantial evidence of potential for abuse, including the data from law enforcement information relevant thereto.

Factor 1: The Substances' Actual or Relative Potential for Abuse

In addition to considering the information, HHS provided in its scientific and medical evaluation documents for DOI and DOC (HHS, 2020), DEA considers all other relevant data regarding the actual or relative potential of abuse of DOI and DOC. The term "abuse" is not defined in the CSA, however the legislative history of the CSA suggests the following four prongs in determining whether a particular drug or substance has a potential for abuse[3]:

a) *There is evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or*

Data show that DOI and DOC have been encountered by law enforcement in the U.S. (Factor 5), indicating DOI and DOC availability for abuse. Based on anecdotal reports (Factor 2), HHS states that individuals are using these substances in amounts sufficient to create a health hazard and are being used for their hallucinogenic activity (HHS, 2020). HHS has determined

[2] 28 CFR 0.100(b).
[3] Comprehensive Drug Abuse Prevention Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970), reprinted in U.S.C.C.A.N. 4566, 4603.

that consumption of DOI and DOC due to their hallucinogenic properties and taking them in amounts sufficient to create a hazard to their health.

b) There is significant diversion of the drug or substance from legitimate drug channels; or

HHS states DOI and DOC are not approved drug products in the U.S. There appears to be no legitimate drug channels for which DOI and DOC can be diverted (HHS, 2020). 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.

c) Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substance; or

According to HHS, DOI and DOC are not found in FDA-approved drug products and practitioners may not legally prescribe these substances, nor dispense them to an individual. Therefore, individuals are taking DOI and DOC on their own initiative, rather than based on medical advice from a practitioner licensed by law to administer drugs. This is consistent with the data from law enforcement seizures and anecdotal reports indicating that DOI and DOC are available "on the street" as illicit substances. DOI and DOC have effects similar to schedule I substances LSD and 2,5-dimethoxy-4-bromoamphetamine (DOB). Thus, individuals have used DOI and DOC on their own initiative rather than on the medical advice of a licensed practitioner, possibly because they are seeking hallucinogenic effects similar to those produced by schedule I substances while simultaneously avoiding the criminal penalties associated with those substances (HHS, 2020).

d) The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug substance will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant diversion from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.[4]

[4] Comprehensive Drug Abuse Prevention Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., sess. 2 (1970); 1970 U.S.C.C.A.N. 4566, 4601.

According to HHS (2020), chemically, DOI and DOC are analogs of the schedule I hallucinogen DOM. The effects and pharmacological action of DOI and DOC are similar to those of other schedule I hallucinogens, such as DOM and LSD, which have no accepted medical use and a high abuse potential.

In drug discrimination studies (an *in vivo* test to assess drug abuse liability of test drugs in comparison to known drugs of abuse) DOI and DOC produce full substitution for the discriminative stimulus effects of DOM, LSD, and *N*,*N*-dimethyltryptamine (DMT, schedule I) (see Factor 2). In humans, anecdotal reports suggest that DOI and DOC produce classic hallucinogenic effects that are similar to DOM, including visual and auditory hallucinations, fatigue, headache, gastrointestinal distress, insomnia and anxiety (Shulgin and Shulgin, 1991; <erowid.org/chemicals/doi/doi.shtml>; <erowid.org/chemicals/doc/doc.shtml>). HHS notes that use of DOC in combination with other drugs is associated with emergency department admissions and one death (HHS, 2020).

As stated by HHS (2020), due to the psychological and cognitive disturbances associated with DOI and DOC, as with other schedule I hallucinogens, it is reasonable to assume that DOI and DOC have substantial capability to be a hazard to the health of the user and to the safety of the community.

Factor 2: Scientific Evidence of the Substances' Pharmacological Effects

As stated by HHS (HHS, 2020), the neurochemical effects of DOI and DOC occur primarily through the serotonergic system in the brain. Hallucinogens are believed to produce their characteristic effects primarily through stimulation of serotonin (5-hydroxytryptamine; 5-HT) 5-HT_{2A} receptors in the brain (Nichols 2004; Eshleman et al., 2014).

In Vitro Studies

Data from *in vitro* receptor binding and functional studies can be used to assess the pharmacological effects related to abuse of hallucinogens. As noted by HHS (HHS, 2020), DOI and DOC have high binding affinity for the 5-HT_2 receptor as evaluated using [^{125}I]DOI as the radioligand to measure binding.

DOI

DOI had a K_d ranging from 0.33 to 3.5 nM in rat frontal cortex homogenates (May et al., 2003; Appel et al., 1990; McKenna et al., 1987; Glennon, 1987) for 5-HT_2 receptors. According to HHS (2020) similar high affinities were also found using rat and human 5-HT_{2A} receptors expressed in GFc6 cells (K_i = 0.6 nM) and A20 cells (K_i = 0.7 nM) (Parish et al., 2005). Using arachidonic acid release to measure cellular function, DOI, like many schedule I hallucinogens,

act as agonists at the 5-HT_{2A} receptor and produce 97% maximal 5-HT effect (EC_{50} = 6.8 nM) in Chinese hamster ovary (CHO) cells (Berg et al., 1998). Further, 5-HT_{2A} receptor also couple to the phospholipase C (PLC) signaling pathway and agonists increase phosphotidyl inositol (PI) hydrolysis. DOI accumulation of PI in A20 cells and GF-6 cells that expressed human 5-HT_{2A} receptors were 44 percent and 77 percent of levels induced by 5-HT, respectively (Parrish et al., 2005).

DOC

DOC had a K_i of 4.0 nM for 5-HT_{2A} receptors in human embryonic kidney (HEK) cells expressing cDNA for human 5-HT_{2A} receptors (Eshleman et al., 2014). DOC increased levels of arachidonic acid (EC_{50} = 2.9 nM) to levels that were 81% of the levels induced by 5-HT and increased PI accumulation to levels that were 102% of the levels induced by 5-HT.

HHS concludes (HHS, 2020), DOI and DOC are agonists at the 5-HT_{2A} receptor, which is likely responsible for their hallucinogenic effects.

Central Nervous System Effects

HHS evaluated the central nervous system effects of DOI and DOC using data from animal studies and reported effects in humans, and concluded that pharmacological effects of DOI and DOC are similar to those of the schedule I hallucinogen, DOM.

Preclinical Studies

According to HHS (HHS, 2020), DOI and DOC have been assessed in some psychopharmacological assays including overt behavior observations and drug discrimination.

Overt Behavioral Responses

According to HHS (2020), overt behavioral effects have been published for DOI, but not for DOC. DOI administration induced an increase in wet dog shakes and back muscle contraction. These behaviors were attributed to 5-HT_{2A} receptor activation since pretreatment with MDL100907, a 5-HT_{2A} receptor antagonist, reduced these behavioral effects of DOI (Baumann and Rothman, 1996; Elmore et al., 2018). HHS notes that since these data show that the overt behavioral effects produced by DOI are mediated by the 5-HT_{2A} receptor and that agonism of the 5-HT_{2A} receptor is the primary mechanism of action of typical hallucinogenic responses together suggest that DOI has hallucinogenic effects.

Discriminative Stimulus Effects

As mentioned by HHS (HHS, 2020), drug discrimination is an experimental method used to determine whether an animal experiences the physiological or behavioral effects of a particular drug as similar to the physiological or behavioral effects of another drug (or class of drugs) to which the animal was previously exposed. DEA further notes that drugs that have discriminative stimulus effects in common with a known drug of abuse are also likely to be abused. Generally, there is strong correspondence between the discriminative effects of drugs of abuse in animals and their effects in humans (Solinas et al., 2006). Thus, drug discrimination is widely used to determine whether or not a drug or substance is pharmacologically similar to a known drug of abuse.

In the preclinical drug discrimination model, a laboratory animal, often a rodent, is trained to press two separate levers based on different stimulus effects of drug versus its vehicle such as saline (or the absence of a drug stimulus cue). After the animals reliably learn the discriminative stimulus effect of the trained drug (e.g., reliably discriminate between the effects of the training drug and vehicle), a test drug with unknown effects is administered. The animals' lever selection indicates whether the novel or test drug is or is not similar to the learned training drug-associated effects. If the novel drug produces ≥ 80% drug-appropriate responding, then the drug is said to have full substitution for the trained drug.

In drug discrimination studies with rats trained to discriminate the stimulus effects of schedule I hallucinogens DOM, LSD, or DMT, DOI (Glennon et al., 1982; Arnt et al., 1989; Chojnacka-Wojcik et al., 1997; Smith et al., 1998) and DOC (Eshleman et al., 2014) fully substituted for each training drug. DOI failed to substitute for amphetamine and methamphetamine in animals trained to discriminate the stimulus effects of these stimulant drugs (Marona-Lewicka and Nichols, 1997; Munzar et al., 1999). DOC also failed to substitute for methamphetamine in methamphetamine-trained rats (Eshleman et al., 2014), but partially substituted for the schedule I substance 3,4-methylenedioxymethamphetamine (MDMA), which elicits both hallucinogenic and stimulatory effects. In addition, in rats trained to discriminate stimulus effects of DOI from saline, the schedule I hallucinogens DOM, DOB, LSD, and DMT produced full substitution for DOI (Chojnacka-Wojcik et al., 1997; Smith et al., 1998; Smith et al., 2003; Marona-Lewicka and Nichols, 1997; Schreiber et al., 1994; Wolf and Leander, 2000).

Based on the drug discrimination data, HHS concluded (HHS, 2020) that these data indicate that DOI and DOC have stimulus properties that substantially overlap with those of the schedule I hallucinogens, DOM, DOB, LSD, and DMT.

Effects of DOI and DOC in Humans

As stated by HHS (2020), clinical studies with DOI and DOC have not been conducted in healthy human volunteers. Thus, there is no data available from standard studies that evaluate

the psychoactive and physiological responses produced by these drugs in humans. However, anecdotal reports of hallucinogenic experiences with DOI and DOC are available in PIKHAL: A Chemical Love Story (Shulgin and Shulgin, 1991), which includes:

> DOI: "This is a clear, clean psychedelic. The eyes-closed imagery is excellent, with clearly delineated patterns, pictures, and colors.... DOI vies with DOB as probably the most potent of the phenethylamine psychedelics as of the moment, and certainly one of the most long lived." < www.erowid.org/chemicals/doi/doi.shtml>
>
> DOC: "This is what I might call an archetypical psychedelic. Everything is there in spades.... This is the works. There are visuals, and there are interpretive problems with knowing just where you really are." < www.erowid.org/chemicals/doc/doc.shtml>

Additionally, HHS reported that anecdotal reports of hallucinogenic experiences with DOI and DOC are available on online drug forums such as erowid.org, in which recreational drug users report on their experiences with all classes of substances. In these reports, DOI and DOC are reported to induce hallucinogenic effects, including prominent visual effects (HHS, 2020).

DEA further notes that WHO critical review of DOC mentions its hallucinogenic effects reported by those that self-experimented with DOC and notes the duration of action may last 12 to 24 hours (WHO, 2019a). WHO notes that the long duration of effects is shared by other structurally related hallucinogens including DOI, DOB, and DOM. DOC is commonly administered orally and/or sublingually when encountered in the form of blotters (WHO, 2019a).

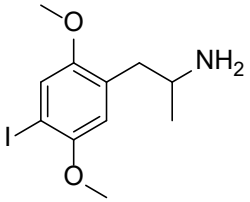
Summary

In summary, DOI and DOC produce psychopharmacological effects (e.g., discriminative stimulus effects) similar to those produced by other schedule I hallucinogens (i.e., LSD, DOM).

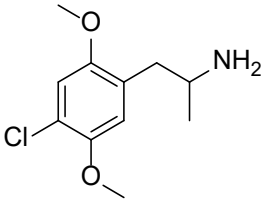
Factor 3: The State of Current Scientific Knowledge Regarding the Substance

DOI and DOC are centrally-acting hallucinogens and part of the phenethylamine hallucinogen family and share structural similarities with schedule I phenethylamine hallucinogens such as DOM. DOI (CAS 42203-78-1) has a molecular formula of $C_{11}H_{16}INO_2$ and a molecular weight of 321.16 g/mol. The hydrochloride salt of DOI has a melting point of 201° C. DOC (CAS 123431-31-2) has a molecular formula of $C_{11}H_{16}ClNO_2$ and a molecular weight of 229.70 g/mol. The hydrochloride salt of DOC has a melting point of 193-194.5° C. WHO reports that DOC is a white, odorless, and crystalline solid (WHO, 2019a).

Figure 1: Chemical structures of DOI and DOC.



DOI



DOC

Synonyms include:

1. DOI – 2,5-dimethoxy-4-iodoamphetamine; 2,5-dimethoxy-4-iodo-phenylisopropylamine; 2,5-dimethoxy-4-iodo-phenylisopropylamine, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, 4-iodo-2,5-dimethoxy-alpha-methylbenzeneethanamine; 1-(4-iodo-2,5-dimethoxyphenyl)propan-2-amine
2. DOC – 2,5-dimethoxy-4-chloroamphetamine; 2,5-dimethoxy-4-chloro-phenylisopropylamine, 1-(2,5-dimethoxy-4- chlorophenyl)-2-aminopropane, 4-chloro-2,5-dimethoxy-alpha-methylbenzene-ethanamine; 1-(4-chloro-2,5-dimethoxyphenyl)propan-2-amine

Medical Use

According to HHS, DOI and DOC are not available in approved human drug products in the U.S. or in any other country and no data are available on their medical use in the treatment of any condition.

Factor 4: History and Current Pattern of Abuse

The history and current pattern of abuse of DOI and DOC are described in law enforcement reports and anecdotal reports use by drug abusers.

In the U.S., law enforcement entities initially encountered DOI and DOC in 2005, according to the National Forensic Laboratory Information System (NFLIS). See Factor 5 for additional information. Each of these phenethylamines is encountered in various forms (e.g., powder, tablets, capsules, liquid, or on blotter paper).

Anecdotal reports on the Internet indicate that individuals are using substances they identified as DOI and DOC for their hallucinogenic effects at sites such as www.erowid.org/chemicals/doi/doi.shtml and www.erowid.org/chemicals/doc/doc.shtml. Importantly, it is impossible to know if the street drugs sold to an individual as DOI or DOC are actually the substances they are marketed as in the absence of chemical analysis or evaluation of biological fluids following ingestion. However, in animal drug discrimination studies (see

Factor 2), DOI and DOC produced effects that are similar to the effects elicited by schedule I hallucinogens such as DOM, LSD, and DMT.

DEA further notes, that based on available abuse data, public health risk, and drug trafficking data, the WHO recommended to the UN that DOC be controlled internationally (WHO, 2019b). In March 2020, the UN Commission on Narcotic Drugs voted to place DOC into schedule I of the 1971 Convention of Psychotropic Substances.

WHO reports that DOC has been available in Europe since 2001. In a report provided by United Nations Office on Drugs and Crime (UNODC) that includes data from their toxicology portal included 16 non-fatal intoxications associated with DOC had been reported internationally, between 2008 and 2017. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported non-fatal intoxications and three deaths associated with DOC (one each in 2015 and 2018, information about the third is unknown). Since 2001, there have been reports of identification of DOC in drug seizures and in collected specimens in Sweden, United Kingdom, France, Norway, Italy, Belgium, Ireland, Slovenia, Spain, Croatia, Denmark, Czech Republic, Luxembourg, and Latvia between 2004 to 2016 in the forms of blotters, powder, and liquid (WHO, 2019a).

Factor 5: The Scope, Duration, and Significance of Abuse

According to NFLIS, in the U.S. there has been significant availability, trafficking, and abuse of a number of phenethylamine hallucinogens including DOI and DOC. This is evidenced by the large numbers of encounters of one or both of these phenethylamine hallucinogens by U.S. law enforcement in a number of states, see Table 5. The exhibits included drug samples in tablet, capsule, powder, liquid, and blotter paper form.

Table 5: Summary of NFLIS[5,6] drug encounters in the U.S. for DOI and DOC.

Drug	Year First Reported	Total Reports	States Where Encountered
DOI	2005	40	CO, FL, IA, IN, KS, ME, MN, MO, NC, OH, PA, TN, TX, WI
DOC	2005	785	AL, AR, CA, CO, CT, FL, GA, IA, ID, IL, KS, KY, LA, MA, ME, MI, MN, MO, MS, NC, ND, NE, NH, NJ, NV, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, WA, WI, WV

[5] NFLIS is a DEA program and a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by federal, state, and local forensic laboratories in the U.S.
[6] NFLIS data were queried on February 23, 2021, by date of submission.

DEA reports that there have been five submissions of DOI and two submissions of DOC reported in the Microgram Bulletins since 2006. Microgram Bulletin is a monthly newsletter published by the DEA Office of Forensic Sciences on the detection and analyses of suspected controlled substances. A fine white powder of DOI was seized at a residence by DEA agents in Michigan (DEA, 2006b). This substance was initially believed to be DOB but it was confirmed by Fourier Transform Infrared Spectroscopy, GC/MS and nuclear magnetic resonance (NMR) to be DOI. A liquid form of DOI was seized by DEA agents from a Madison Resident Office in 2007 (DEA, 2007). In three other law enforcement encounters, DOI was on blotter paper (DEA, 2006a; 2008a; 2008b). Analysis of a methanol extract indicated that the substance in all three incidents was DOI. The samples were analyzed by the Florida Department of Law Enforcement's Orlando Regional Crime Laboratory in 2006 and the Palm Beach Crime Laboratory, and Kentucky State Police Western Laboratories in 2008. In two law enforcement encounters, DOC was on blotter paper (DEA, 2009a; 2009b). Those samples were analyzed by the Georgia Bureau of Investigations Central Regional Crime Laboratory and Kansas' Bureau of Investigations West Region Laboratory in 2009.

Factor 6: What, If Any, Risk to the Public Health

HHS states that the public health risks resulting from the abuse of DOI and DOC, as with any hallucinogen, relate primarily to their ability to induce hallucinogenic effects and other sensory distortions, impaired judgement, and strange or dangerous behavior (Nichols, 2004). To date, there are no reports of distressing responses or death associated with DOI in medical literature. There have been three published reports in years 2008, 2014, and 2015 of adverse events associated with DOC.

As HHS reports, one case involved a 20-year-old man who attended a rave party. After ingestion, the man collapsed with tonic-clonic seizures and reduced consciousness (Ovaska et al., 2008). He was taken to an emergency department and was intubated in transport. Upon arrival, the individual was unresponsive with sinus tachycardia, hypertension, dilated pupils nonresponsive to light, and rhabdomyolysis. After being under medical care for 22 hours, he was released without apparent sequelae. This individual had reportedly ingested MDMA and DOI, but a toxicological analysis determined he had taken MDMA and DOC. In a 2014 report, a 37-year-old man who had a history of methamphetamine abuse was found dead at home. A toxicological analysis of his urine and peripheral blood were both positive for DOC and caffeine, but no other drugs (Barnett et al., 2014). In the third report (Burish et al., 2015), an 18-year-old man experienced hallucinations and agitation, followed by seizures, shaking in extremities and dilated pupils. Subsequently, he was intubated due to experiencing sinus tachycardia, hypertension, tachypnea, and rhabdomyolysis. A toxicological report showed he had taken cannabinoids and opioids in addition to DOC.

In summary, HHS states that these reports demonstrate that adverse events and death can occur from the use of DOC. In addition, HHS concludes that since DOI is structurally similar to

DOC and produces similar effects to DOC, it is likely that it may produce serious adverse effects similar to DOC. Thus, serious adverse events that may include death represent a risk to the individual drug user and to public health.

Factor 7: Psychic or Physiological Dependence Liability

According to HHS, the physiological dependence liability of DOI and DOC in animals and humans is not reported in scientific and medical literature. Thus, it is not possible to determine whether DOI and DOC produce physiological dependence following acute or chronic administration.

However, HHS states that DOI and DOC and other related phenethylamine hallucinogens (such as the schedule I substance, DOM) are highly abusable substances. Drug discrimination studies in animals indicate that DOI and DOC fully substitute to the discriminative stimulus effects of schedule I hallucinogens DOM, LSD, and DMT (see Factor 2). HHS notes that, hallucinogens are not usually associated with physical dependence, likely due to the rapid development of tolerance (Buckholtz et al., 1990) precluding daily administration. Hallucinogen abusers may develop psychological dependence as evidenced by the continued use of these substances despite knowledge of their potential toxic and adverse effects (HHS, 2020).

Factor 8: Whether the Substance Is an Immediate Precursor of a Substance Already Controlled

DOI and DOC are not immediate precursors of a substance already controlled under the CSA as defined by 21 U.S.C. 802(23).

III. Findings for Schedule Placement Pursuant to 21 U.S.C. 812(b)

21 U.S.C. 812(b) requires the evaluation of a substance's abuse potential, accepted medical use, and safety for use under medical supervision for placement in the CSA as a controlled substance. After consideration of the eight factors determinative of control of a substance [21 U.S.C. 811(c)], and a review of the scientific and medical evaluations and scheduling recommendations provided by HHS, DEA finds that DOI and DOC and their salts meet the following criteria for placement in schedule I of the CSA, under 21 U.S.C. 812(b)(1).

1) The drug has a high potential for abuse.

HHS mentions that DOI and DOC are phenethylamine hallucinogens with high potential of abuse that produces pharmacological effects qualitatively similar to those of DOM, a schedule I hallucinogen. HHS states that in drug discrimination studies, both DOI and DOC fully

generalize to the discriminative effects produced by DOM. In humans, DOI and DOC produce classic hallucinogenic effects such as hallucinations, similar to the effects in humans elicited by DOM, a schedule I hallucinogen. Law enforcement reported a number of encounters of these substances. Law enforcement first encountered DOI and DOC in 2005.

2) The drug has no currently accepted medical use in treatment in the United States.

According to HHS, FDA has not approved a marketing application for a drug product containing DOI or DOC for any therapeutic indication. In addition, DEA and HHS know of no clinical studies or petitioners, claiming an accepted medical use in the U.S. Therefore, DOI and DOC have no currently accepted medical use in treatment in the U.S.

3) There is a lack of accepted safety for use of the drug under medical supervision.

HHS states that the use of DOC is associated with serious adverse consequences including deaths. Since DOI is structurally similar to DOC and produces effects similar to DOC, it is likely that DOI may produce serious adverse events similar to DOC. Since DOI and DOC have no currently accepted medical use and have not been thoroughly investigated as new drugs, their safety for use under medical supervision is not determined. Thus, there is a lack of accepted safety for use of these substances under medical supervision.

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