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PERSPECTIVE

WILEY

The origin of 2,5-dimethoxy-4-methylamphetamine (DOM, STP)

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Abstract

The story of the 1967 appearance of the powerful psychedelic 2,5-dimethoxy-4-methylamphetamine (DOM, STP) commonly omits details and often includes hyperbole and inaccuracies. It is well known how and when the drug was first distributed to the public for free by Owsley Stanley, but the role that Alexander Shulgin played in providing that material is not as well understood. In the interest of transparency and historical accuracy, this article attempts to present an accurate account of this well-known but inadequately detailed event. It follows DOM's development as an experimental substance believed to hold potential promise in psychotherapeutic applications through its appearance as a street drug generating bad press and a lasting bad impression among the public. One of the more interesting questions is why Shulgin would have taken such an immense risk in releasing this material to clandestine operators. While DOM was still legal it was also Dow's intellectual property, so discovery of his involvement could have jeopardized his career. The escape is especially curious as all fingers would logically first point towards Shulgin as the source. Drawing from published and unpublished sources, the authors attempt to suggest answers. DOM rapidly faded into oblivion before human pharmacodynamics and pharmacokinetics could be established. In this account, the reader is informed of the potential value that the compound played in non-clinical molecular neuroscience, elucidating receptor specificity of new drugs, and how mistaken warnings about combining DOM with chlorpromazine led to better non-pharmacological drug crisis response.

KEYWORDS
DOM, Owsley, psychedelic, psychotomimetic, Shulgin

1 | INTRODUCTION

In 1967, a then unknown drug appeared in San Francisco under the street name of STP. The appearance was almost characterized by what was not known about it. Users, law enforcement, and medical authorities did not know its identity or its properties beyond being told it was a powerful hallucinogen similar to LSD but longer lasting.[1,2] When its intense effects and long duration sent some panicked users in search of medical attention out of concerns that they were not coming down, medical professionals also knew nothing about it, and there was much initial confusion resulting in wild speculation.[3,4] Due to the efforts that were made both by the media and by medical doctors to deliberately scare users away from STP with hyperbole, it is not possible to determine the actual extent of the problem. Meyers estimated that a total of around 60 people had sought professional attention out of a crowd that he purported had been given 5000 tablets on June 21, 1967.[5] Meyers noted that thirty-two people visited Haight Ashbury Free Medical Clinic[5] (twenty by the end of June[6]) and

another thirteen showed up at the emergency room at SF General.[5] Most of the people seeking help at HAFMC received supportive words, occasionally with mild sedation, before being sent home within a few hours but one was hospitalized with a serious psychotic episode.[5] Psychotic reactions were also noted among the patients hospitalized at SF General. It was soon determined to have come from experimental research but how it came to escape was also mysterious.[2]

Much has been written about that subject in scientific journals, publications written for a popular audience, and in news accounts. New information has appeared in public revelations by Nick Sand and Tim Scully, and additional documentation emerged during the digitization process for the Alexander Shulgin Archiving Project, October 2015 through July 2022. This offered the opportunity to fill in some of the missing details and provide a more accurate account of its appearance as a street drug.

This account is not a simple review of the available published information although it does include some of the primary work and literature. It also draws from unpublished research notes, documents and correspondence in Shulgin's possession, and conversations with underground chemists Owsley Stanley III, Timothy Scully, and Nicholas Sand. As such, it adds a more transparent account to what presently exists. Many gaps of understanding remain, but this analysis addresses some of them.

To respect privacy, most personal names other than published authors have been redacted.

1.1 | The participants

The molecule 1-(2,5-dimethoxy-4-methylphenyl)propan-2-amine is a psychedelic amphetamine invented by Alexander T. "Sasha" Shulgin in 1963, during his search for new psychiatric medicinals while at Dow Chemical.[4] It appeared on the streets in 1967 as an "LSD substitute," with the name of STP abbreviating "Serenity, Tranquility and Peace"[7] (Figures 1 and 2). Additional assignments for the acronym exist, but this was the original. Shulgin's shorthand code was DOM, abbreviating "des-oxy methyl" with respect to its relationship with 1-(2,4,5-trimethoxyphenyl)propan-2-amine (TMA-2).[4] We will also discuss a closely related homolog, DOET (1-(2,5-dimethoxy-4-ethylphenyl)propan-2-amine). DOM was initially known as K-61,082.[8]

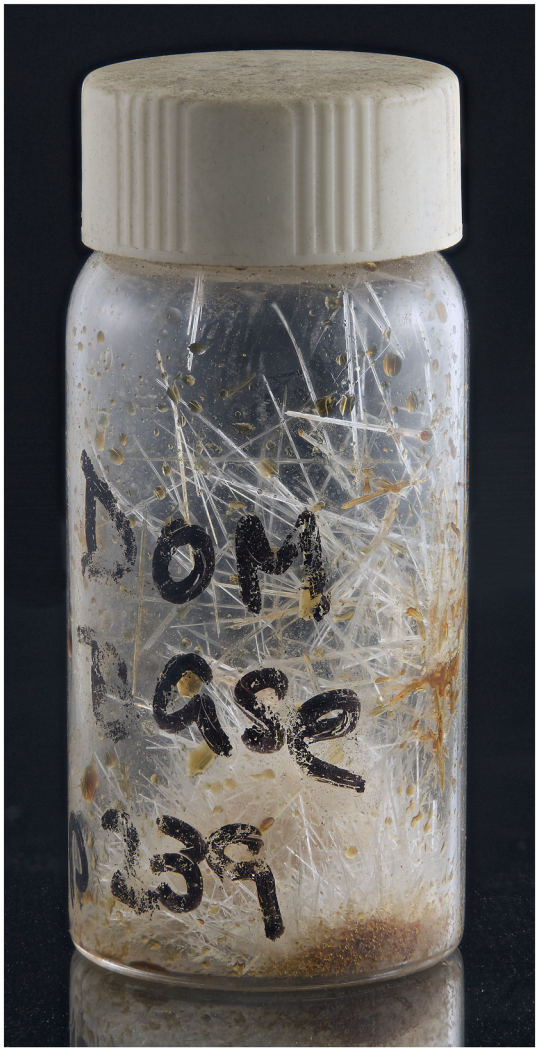

FIGURE 1 DOM crystals. Photograph by Paul Daley.

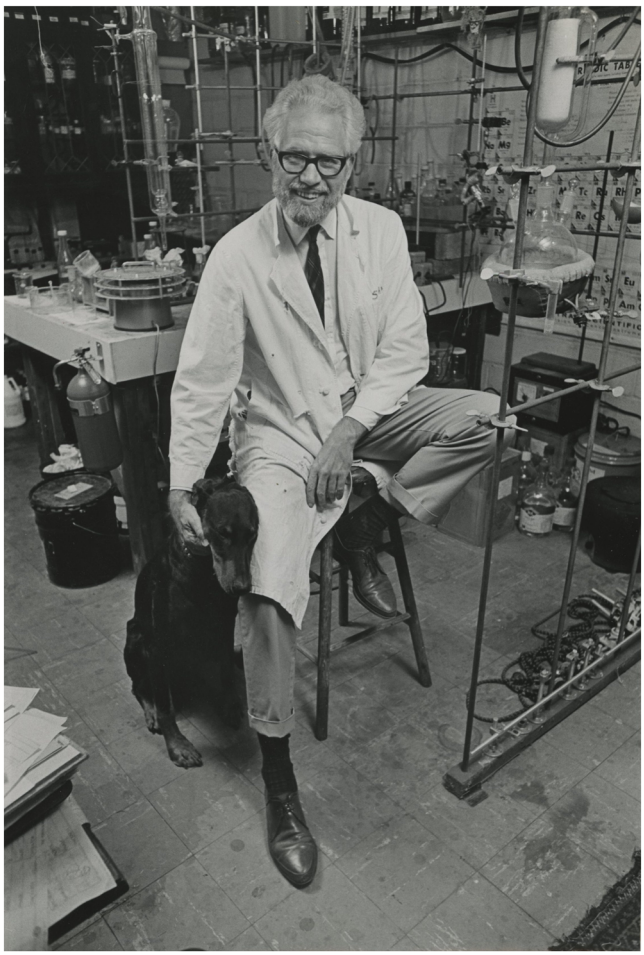

FIGURE 2 Sasha and Lance. Photograph by Dennis Galloway.

It was later referred to by Shulgin as "my hair shirt"[9] suggesting that the molecule had created a sense of personal discomfort for him.

Alexander T. Shulgin (June 17, 1925–June 2, 2014) was a chemist and pharmacologist who discovered and/or uncovered nearly 200 psychedelics during his career: first, during the early 1960s while working for Dow Chemical and, later, during the course of his independent research.[4]

Owsley Stanley III was a well-known producer of LSD before it was made illegal.[10] His birth name was Augustus Owsley Stanley III, but he dropped Augustus, legally changing his name in 1967. During a short period of time, Stanley believed STP could serve as a legal replacement for LSD.[11,12] He had taught his protégé Timothy Scully, a brilliant electronics engineer, how to make LSD, and now tasked him with converting the reactions shown on an index card provided by Shulgin into a process they could use to manufacture DOM. Stanley later told Scully to show their associate underground chemist Nick Sand how to make DOM.[11,12] Sand went on to make a "prodigious amount" of the drug (Data S1 https://sacredcacti.com/supplemental/).

2 | HUMAN EFFECTS OF DOM

DOM is a stimulant at lower dosages and a hallucinogen at higher levels.[4,13–15] Smith in 1969 described DOM as producing psychological effects similar to those resulting from LSD use, with "significant alteration in perceptual functioning producing vivid, colored imagery and impairment of cognitive functioning or reality testing."[16] Lingeman differentiated DOM from LSD by noting that even though DOM was reported to be more intense and longer lasting than LSD, it caused less disorientation and loss of ego function than LSD and allowed users to engage in basic functions that can be difficult when under the influence of LSD (such as answering a telephone or finding a cab).[17] Shulgin noted that DOM could also produce paradoxical states such as a person feeling happy and sad at the same time and to be highly influenced by set (a person's state of mind, personality, and expectations) and setting (auditory, visual, tactile, or other influences from their environment).[18] "Under the influence of DOM the individual may experience visual imagery, distortions in time perception, feelings of depersonalization, rapid mood changes, alterations in body sensations and increased thought processes often laden with deep emotional meaning." Users may feel like they are overwhelmed or losing control; especially if they are inexperienced.

DOM has a much greater potency than mescaline though published estimates vary. For example, Shulgin himself gave mescaline equivalency estimates of 80x,[19] >100–120x,[20,21] and 150x[22]; Snyder and coworkers gave 60–100x.[14] These "mescaline equivalency" numbers have minimal value outside of broadly comparing relative potencies and they can also be confusing and potentially misleading.

One to four milligrams of DOM produces euphoria and enhanced self-awareness with the appearance of some perceptual disturbances as the dosage level increases.[4,13] Psychedelic effects manifest at levels above 5 (Hollister et al.[15]) to 7 (Scully[12]) mg. The onset is prolonged, with first alerts in 30 min and the appearance of intense peak effects developing over the course of the next 3–5 h.[15] (Snyder gave the onset as 60–90 min; perhaps reflecting the use of smaller dosages than Hollister?[14]) Effects are long lasting, but there are conflicts in the reported accounts. Durations of 24 h or greater are suggested in the news accounts of the day,[1,2,23] including the first note in the press prior to its appearance.[24] Doctor David Smith of the Haight-Ashbury Free Medical Clinic alleged that a user might experience "vivid-and often terrifying hallucinations that may last for three or four days" during his successful effort to scare people away from the drug.[3]

A small dose will dissipate in 8 h or less, but the effects of a normal hallucinogenic dose can last around 16 h.[14] It is unclear how many of the claims of longer durations may be hyperbole, reflect the outcome of ingestion of larger dosages, may involve individual metabolic differences, or are the result of personal definitions that include lingering residual after-effects. Other factors such as polydrug use can also affect duration. In his early notes at Dow, Shulgin gave the duration as 24 h[13] but later revised this to 16–24 h.[19] In their renowned PIHKAL, the Shulgins reported the duration as 14–20 h.[4] Snyder,[14] Faillace,[25] and Hollister[15] were unable to reproduce a duration of 24 h in any of their controlled studies of DOM in humans, despite the latter using up to 14 mg. One of Snyder's patients did report "feeling high" for 2 days afterwards.[14] Faiilace reported 2.7 and 3.3 mg lasted 5 to 6 h[25] with Hollister commenting low doses were completely resolved by 7 h.[15] In 1970, Snyder gave the duration as 6–8 h.[26] The Institute for Contemporary Studies noted an average duration of 8 to 15 h in humans with 5 or 10 mg dosages.[27] It has been suggested that higher dosages may be responsible for outcomes reporting longer duration of effects,[15,28] yet this matter is presently understudied and is not supported by the clinical evidence in humans. Nevertheless, there are too many anecdotal accounts to dismiss. One of the authors (KT) was told by Stanley that his first experience was excessive when three doses were taken over the course of a couple of hours due to his growing impatience over its unexpectedly slow onset. The result was described as 3 days of hell. In one of the few references to a very high human dose, in 1968, a 4-year-old child was found convulsing after ingesting what was thought by his parents to have been as many as 40 tablets of DOM.[29] The outcome is not known but an included comment suggested that the child had not fully recovered after 2 days. "After two days he was able to respond to questions. Whether he will fully recover is unknown at this time."[29]

While it is common in toxicological studies for high dosages in animals to follow a normal time course,[30] there is some experimental support suggesting longer effects can result from higher dosages.[15] Despite being unable to reproduce these long durations of 24 h or more, Hollister's work with humans showed their subjects recovered faster from smaller dosages than larger ones.[15] Similarly Reynolds reported observing a longer duration in chimpanzees with increasing dosage: 5 mg lasted 5 h while 10 mg lasted up to 8 h.[31] However, we have been unable to locate any study in animals or humans reporting drug effects lasting 24 h or more.

The potency of DOM arises from several structural elements. The presence of a methyl group in the alpha sidechain position is believed to produce a more powerful substance by protecting the basic

nitrogen from deamination.[32] The 4-methyl moiety on DOM is believed to further interfere with its metabolism by preventing 4-demethylation as had been shown to occur with mescaline[33] and 3,4-dimethoxyphenethylamine.[34] In Shulgin's discovery disclosure in 1965, interfering with this known metabolic route was given as his underlying rationale for making a 4-substitution choice that was not metabolically labile.[8] The lengthy duration may additionally involve the formation of two active metabolites, 1-(2-hydroxy-5-methoxy-4-methylphenyl)propan-2-amine and 1-(5-hydroxy-2-methoxy-4-methylphenyl)propan-2-amine.[35,36] These have been suggested to have greater effectiveness at behavioral disruption in rats than DOM.[35] Their effects would be perceived of as a second intensity peak beginning when a user would typically anticipate a drug to be wearing off. This suggestion may be supported by the metabolism of DOM reported in rats by Zweig and Castagnoli[36] and Eckler[35] but is presently remains unproven for humans due to scant and inadequate studies of DOM's metabolism in humans. Shulgin also voiced suspicions of DOM producing an active metabolite in humans.[4] Snyder observed that only between 5% and 10%[34] or 5–20%[14] of an administered dose of DOM was excreted unchanged, suggesting that significant levels of metabolism may occur in humans.

Notwithstanding DOM's long duration, the claims of trips lasting 72 h or longer[1–3,23] (which include experiences voiced by reliable reporters) may be apocryphal or they raise some questions that currently appear to be unresolvable. Similarly the lack of descriptions of a second peak appearing in any of the clinical testing in humans also raises unresolved questions about that belief.

3 | ANSWERS CREATING QUESTIONS

The relatively short-lived appearance and availability of DOM as the street drug STP (primarily during 1967–1973)[29,37–39] has long included some elements of mystery.

Public revelation of Shulgin's role in the appearance of STP first occurred in 2010 when the prolific underground chemist Nick Sand told the story of how DOM was released and became STP after the route for its synthesis was given to Stanley by Shulgin, written on an index card.[40] This STP origin story was part of Sand's 2010 presentation at the Multidisciplinary Association for Psychedelic Studies (MAPS) "Psychedelic Science in the 21st Century" conference in San Jose, CA. Sand mistakenly believed that Shulgin would appreciate the intended accolade. Additional details which were not mentioned by Sand were added in 2019, during an interview with Sand's associate Tim Scully.[41] These included a revelation regarding a 50 g sample of DOM accompanying the index card.

4 | THE EARLY HISTORY OF DOM

Two closely related compounds, DOM and DOET, were invented around the same time in 1963 at Dow Chemical by Shulgin and presented for patenting and further study.[8] The designs of this group of compounds were inspired by the structure of mescaline, and the discovery of TMA (3,4,5-trimethoxyamphetamine), that had roughly twice the potency of mescaline and a distinct pharmacology.[22] Among the numerous compounds synthesized in this program, DOET was a very closely related 4-ethyl homolog that was initially referred to as DOE,[8] later changed due to the prior use of the latter acronym for methamphetamine (desoxyephedrine).[42] DOET played important roles in the history of DOM, which merits further discussion around these two substances together.

They both impressed Shulgin greatly even though he recorded personally ingesting DOM only within a barely threshold dosage range during those early years of 1963 and 1964.[13,43] His 15-year-old son Theodore "Ted" Shulgin helped in the birth of DOM by performing the first step in its initial synthesis late at night at Dow on June 22, 1963, during a brief period of the son's interest in chemistry (noted on page 76 of Shulgin's lab book[44] and described in an unpublished article on DOM[9]). Shulgin turned Ted's aldehyde into the corresponding nitropropene on July 7, 1963, and completed the synthesis by reducing it to the amine on November 30, 1963 (see pages 91 and 178 in Shulgin[44]). Shulgin first ingested 200 μg of the new molecule at 3:22 the next afternoon as a divided dose spaced 80 min apart. In a note (page 84),[13] he observed that it produced almost no effect.

On January 4, 1964, Shulgin tried 1 mg, taken as 400 μg, followed by another 400 μg an hour later, with 200 μg added 2 h and 10 min after the first dose.[13] This hinted at activity, so he followed it 5 days later with 1.6 mg and, on pages 88–89 in his lab notes, described experiencing threshold effects.[43] This figure is given as 1.4 mg in the summary on page 84,[13] but it was recorded as 1.6 mg in the handwritten bioassay account on page 88.[43]

A friend and research collaborator, Thornton W. Sargent, was the first person to take DOM at what was described as a "hallucinogenic" level on February 3, 1964, with 2.3 mg.[45] Sargent's handwritten account on February 4, 1964, described mood elevation and enhancement of color perception. "The emotional content and empathy for others was closer to mescaline than amphetamine."[45,p93] Before long, another coworker ("W") reported the first clearly psychedelic experience after ingesting 4.1 mg on November 6, 1964.[46] A semi-fictionalized account appears on pages 53–56 in PIKHAL.[47] The observer of "W" recorded that a pleasant experience had occurred after ingesting 4.1 mg.[46] The subjects described "fragile hallucinations" with pulsating pastel colors appearing around 6 h into the experience.

Shulgin wrote a preliminary project report about DOM for Dow in February of 1965 in which he described its effects in humans and its potency.[48] Shulgin hoped an Investigational New Drug application (IND) would be submitted and urged Dow to patent both drugs.[48] There were concerns raised by the patent department that were included in the invention disclosure, about the existence of "prior art" published by Marsh & Herring in 1950[49] describing the pharmacology of 4-methyl substituted amphetamines. However, this earlier disclosure did not prevent Shulgin from successfully obtaining patents on both DOM and DOET in England in 1969[50] and in the United States in 1970.[51]

4.1 | Interest beyond Dow

During discussions between Snyder (Johns Hopkins) and Shulgin on February 15, 1965, comments were made alluding to the existence of new molecules of potential interest to Johns Hopkins.[52] At that time, DOM and DOET were not explicitly identified or described to him. This occurred while they were discussing structure–activity relationships of six molecules that the Johns Hopkins group was evaluating: TMA-1, TMA-2, TMA-3, MMDA-1, MMDA-2, and MMDA-3a.[52]

Earlier conversation between Shulgin and Snyder on January 21, 1965, addressed the potential value of other phenethylamines.[53] Even before there was any ability for Shulgin to discuss actual details about the new and unpublished compounds without prior authorization by Dow's patent department, Snyder had already initiated a request for evaluation samples from Dow.[53]

Additional information about the activity of DOM and DOET was shared in a conversation between Shulgin and Snyder on August 15, 1966, while at a conference at the Stanford Research Institute.[54] A request to Dow for samples of DOM and DOET soon followed on August 31, 1966,[55] along with a conversation discussing the possibility of Shulgin spending a 1 year organic chemistry research sabbatical at Johns Hopkins while they evaluated his new molecules.[55] The sabbatical did not occur and Shulgin instead entered a post-doctoral fellowship at the University of California, San Francisco, Langely Porter Psychiatric Institute in 1967.[56]

While an IND was only submitted for DOET,[5,57] the psychiatry department at Johns Hopkins was aware of both molecules as they were planning preliminary work with them after writing to Dow about this possibility.[55] They also had a conversation with Dow during August 1966 in which Snyder commented "The preliminary pharmacology of DOM and DOE[T] described in these reports indicates that they are remarkably potent and possess properties which may be of considerable use in clinical psychiatry."[55] A record of a conversation between Snyder and Shulgin's research supervisor noted that Snyder "… was very interested in the high activity of DOM and DOE(T) and in the reported nature of this activity. He stated that there could be a very large market for drugs that would be effective for relief of neurotic depression …" Snyder added that the head of their psychiatry department, Joel Elkes, "would probably welcome the opportunity to carry out a clinical study at Johns Hopkins on DOM or DOE(T)."[54] Approvals soon followed and Dow sent samples during October 1966.[57,58] Snyder sent Dow proposed research protocols on November 26, 1966,[59] adding a proposed budget on December 11, 1966.[60] The Johns Hopkins group received a visit from a Dow representative to discuss this subject on December 7, 1966.[61]

Dow sent 10 g of DOET and 10 g of DOM to Johns Hopkins in October 1966 with eventual plans for clinical trials in humans.[39,58] Both were intended for acute double-blind trials in humans,[62] and an application for an IND exemption was sought.[63] Despite Snyder expressing interest in both compounds as late as August 17, 1966,[54] Dow took only DOET further than DOM.[59] Owing to the costs involved, it is common for drug companies to synthesize compounds that are not developed further and often evaluate multiple closely related drugs but take only one of them into clinical trials. We suspect Johns Hopkins may have only wanted to budget for the evaluation of a single drug rather than committing their financial and human resources to performing two parallel clinical studies. Also DOET was perceived as not being as hallucinogenic as DOM, which may have influenced their decision. However, we do not have access to either institutions' final call. We can only speculate this was the rationale for DOM being dropped and Johns Hopkins presenting a protocol and budget only for DOET.[59,60] Conversations between Snyder and Shulgin[64] document concerns voiced by Dow about the ratio between a therapeutic dose and a hallucinogenic dose (i.e., therapeutic index). Snyder observed[14] that DOET "appears to produce subjective effects such as mild euphoria and enhanced self-awareness in the complete absence of any psychotomimetic or hallucinogenic actions." It is notable that in all of the human trials by Snyder and coworkers, the dosage levels of DOET were kept to a sub-hallucinogenic range, and it was described as lacking hallucinogenic activity.[34,65]

4.2 | Toxicology studies

Early in 1966, 100 g of DOET was sent to Dow's Biochemical Research Laboratories, in Midland, Michigan, for animal toxicology studies.[20] These were also performed for DOM, but there are questions concerning the details. They are mentioned in Shulgin's *Pharmacology Book 1* as having occurred in 1964 at Dow in Midland,[66] but another date also appears in the literature attributed to Dow. Spindler and Garcia Monge had acquired DOM employed in their study directly from Dow.[67] They reported an LD_{50} value for DOM of 60 mg/kg in rats though the administration route was not given (they cited Dow Chemical, DOM Data Sheet dated October 10, 1967).

During the creation of a review article about DOM in 1973,[18] Shulgin wrote to Dow to inquire about acquiring a copy of these toxicology reports and was informed that he should ask FDA as they were not available from Dow.[68] He made the same request of the FDA on July 16, 1973,[69] but never obtained copies. There is no indication that he ever received a reply. Our efforts attempting to acquire this material as part of the Shulgin Archive digitization project have similarly been unsuccessful. The only available data raised more questions about the origin of that LD_{50} value. In the animal pharmacology notes included by Shulgin, preliminary animal testing of DOM by Dow in 1964 had reported that 40 mg/kg/ip in Swiss Webster mice caused no deaths, 60 mg/kg/ip to cause death in 33% of them, and 80 mg/kg/ip to be an LD_{100}.[66]

There are other known inconsistencies in the reported toxicity data for DOM. Cayman Chemical Company includes 70 mg/kp/ip/mouse as an LD_{50} for DOM base in their 2022 Safety Data Sheet.[70] LD_{50} values reported by Davis for the hydrochloride included mouse, 36 mg/kg/iv and 330 mg/kg/po, and rat, 32.5 mg/kg/ip.[71] However, Davis had earlier reported no deaths in female Swiss-Webster mice given 63 mg/kg/ip, and their graphical depiction of an LD_{50} is closer to 100 mg/kg.[72] Similarly, Leonard employed up to 60 mg/kg/ip in

metabolic testing using Aldrich-Park rats.[73] This dosage level produced agitation, with convulsions in some animals, but no fatalities.

4.3 | Sharing knowledge

On December 11, 1965, Shulgin was told by Dow that it might be helpful if Snyder was provided with a summary of the limited human data that existed, and he sent a letter to Snyder the following day with most of that information.[58] In a phone conversation with Dow on December 20, 1965, Snyder confirmed that his expectations about DOET were unchanged after reading Shulgin's accounts.[57]

Snyder was still expressing interest to Dow about Johns Hopkins exploring both molecules in humans as late as August 17, 1966.[54] When the proposed research protocols were submitted to Dow on November 26, 1966, only DOET was mentioned.[59]

On November 3, 1966, the director of the Johns Hopkins Department of Pharmacology and Experimental Therapeutics, Paul Talalay, asked Shulgin if he would give a talk to his department.[74] Shulgin's request for permission from Dow's patent department to give the presentation has not been located. Their approval was explicitly required for all talks and publications involving his discovery of patentable molecules.

The talk was entitled "The syntheses and psychotomimetic evaluation of several bases related to mescaline."[22] A request from Talalay was received on November 26, 1966, asking that the talk include information on their synthesis, which he felt would be of interest to the members of their chemistry department who would also be present.[74] In a letter sent to Snyder on January 12, 1967, Shulgin commented "Although there will be quite a few chemical structures presented, most of the synthetic detail has been phrased only in general terms, with more of the emphasis placed on the structure-activity relationships, and the underlying rationale that led the study through its several interesting byways."[75]

On January 20, 1967, Shulgin received written permission from Dow's patent department for a single oral presentation.[76] His Johns Hopkins lecture was given the morning of January 25, 1967.[22] This was the lecture that Shulgin later suggested was the point of initial public disclosure of the structure of DOM and its synthesis.[42] In one such recounting, in correspondence to a journalist in 1984, he commented, "Early in 1967, I had given a rolling seminar at Johns Hopkins, in Baltimore, and had discussed the chemistry and activity of it. (...) The audience was a mixed collection of types; this may have been the source of the details."[77]

His talk was well received. Talalay wrote him on February 6 to thank him for his "most interesting and excellently presented seminar."[78]

4.4 | Leaving Dow

Shulgin gave his notice to Dow during December 1966 and left at the end of the month to further his education in psychopharmacology.[57] This seemed to have come as a surprise to his superiors, but he left Dow on good terms. His resumé notes that during 1967–1968, he had accepted and completed: "a post-doctoral fellowship in the Interdisciplinary Training Program at the University of California Medical School in San Francisco which gave him the opportunity to study in the Department of Pharmacology, and in the Department of Psychiatry at the Langley Porter Neurological Institute. Since the completion of this fellowship, he has continued his active interest in psychopharmacology."[56]

5 | DOM REACHES THE PUBLIC AS STP

Words about DOM appeared in the first issue of *Microgram* in November of 1967, by the Bureau of Drug Abuse Control (BDAC).[28] They commented about hearing of a new drug, "STP," during the spring of that same year and acquired their first tablets in April 1967. There was also a public announcement in the April 28 1967, *Berkeley Barb*, mentioning that a new drug called STP that "lasts four times as long as acid" was soon to be on the street.[24] Though an exact date has been elusive, late January following Shulgin's Johns Hopkins talk appears to have been the earliest point that he would have given DOM to Stanley. It is certain that this must have occurred either before or sometime early in February 1967, based on the first bioassays known to Tim Scully being in early February.[11] An important element in this story is that Shulgin did not include any actual instructions or provide subsequent technical advice to Stanley. According to the information in his archives, Scully learned how to perform the synthesis through his own library research.[11,12] This is particularly noteworthy for our story as this delayed Stanley's ability to produce the molecule by a few months making it evident that he could not have possessed DOM in time for it to be given away at the summer solstice celebration.

While the Johns Hopkins talk and its contents had been cleared with Dow's legal department, the only internal literature existed at Dow on DOM in January of 1967.[28,79–82] Nothing had been published. Even the pharmacology notes that had been shared with Snyder did not mention its identity beyond the acronym DOM.[58] This is a central element in this story; no one outside of Dow knew anything about the actual identity of DOM until the Johns Hopkins talk occurred in January of 1967.

STP made its memorable appearance when Stanley gave away up to several thousand tablets at no cost to attendees of a San Francisco summer solstice music festival in Golden Gate Park on June 21, 1967.[11,12] Other authors have purported higher numbers such as 5000[5] or even 10,000[82] doses were given away that day but those are not based on reality.[11] Some of these contained 10 mg and a smaller number contained 20 mg of what was then an almost unknown drug.[3,6,7,11,12] Numerous concerned people sought medical attention, fearing they were not going to recover.[6,16,83] Matthew Baggott provides an excellent account of DOM's escape and a rational assessment of the aftermath. We refer readers to that article for more details.[7]

Apparently, the IND for DOET that had been submitted to the FDA enabled the identification of STP as being something very similar.[28] A report of the FDA noting STP had similarities to mescaline appeared in the press on June 30, 1967.[84] On July 25, 1967, Shulgin replied to a fellow researcher in Europe who had shared a UK newspaper report on the appearance of a new drug in the USA: "I have learned from people in the Pharmacology Department in San Francisco that the FDA has identified the material as a dimethoxymethylphenylisopropyl amine. Thus is it highly possible that this substance is my extremely potent psychotomimetic DOM, or a very close analog to it." He commented further that the structure was still unpublished but noted he had "talked quite widely about them in seminars and such."[85] Shulgin had already publicly speculated on the possibility it might be one of his molecules on July 7, 1967, adding that the lengthy reported duration suggested a connection to DOM.[85]

At some point during their investigation, FDA contacted Dow for confirmation that it was their molecule. The exact date when this occurred is not available, but it was widely reported by the press beginning in early August of 1967.[79–81] The news of Dow being the point of origin appeared in newspapers beginning on August 3, 1967,[79–81] and in *Chemical & Engineering News* on August 14, 1967.[86] Shulgin was soon identified as being its "developer" and was interviewed by Peter Vogel for an article in August 25, 1967, edition of the *San Francisco Chronicle* in which he "denied being responsible for leaking STP to the public."[87] Leo Hollister, with the Veterans Administration Hospital at Menlo Park, CA (Department of Veterans Affairs, VA), had also received DOM for human investigation in 1967.[14,15] The source of this DOM was not specified by either Hollister or Snyder. It is not known whether this work involved the same material Johns Hopkins received from Dow, intended for acute clinical trials in humans,[59] or whether Hollister had been provided with additional DOM by the FDA or by Dow.

Snyder noted that both the human study of DOM at Johns Hopkins and that of Hollister at the VA were requested by the FDA.[14] The BDAC made supportive comments on this effort in the first issue of *Microgram*, but their account did not identify the researchers.[28] No reference was made to Johns Hopkins having already been provided with DOM by Dow late in 1966.

The first reports from Snyder made no mention about the activity of DOM already having been established by Shulgin and coworkers, or of Snyder's pre-existing knowledge of the drug.[14,65] He later expressed remorse and was apologetic to Shulgin about this omission[64] as Snyder had received credit for establishing its activity in humans rather than Shulgin, and this persisted in the literature.[67]

6 | POTENTIAL MOTIVATIONS FOR SHARING DOM WITH OWSLEY

Why would Shulgin have taken such a great personal risk to see DOM become available? Had his role been discovered it would have ended his career and it could have caused him lasting legal difficulties. DOM was not a controlled substance until it was "placed under control" on April 2, 1968,[37] so that was not the immediate concern.

The release of DOM is especially curious as all fingers would invariably first point to Shulgin. After all, this was a molecule that was still unpublished.[28] It was also Dow's intellectual property even though at that time it was not yet patented. It was on record as having been invented by a former Dow employee, namely, Shulgin.[8] Up until the presentation at Johns Hopkins on January 25, 1967,[19] not even the structure of the molecule had been published outside Dow's internal literature.[28] Very few people knew anything at all about it outside a small circle including Shulgin, other employees of Dow, and less than a handful of people at or working with Johns Hopkins, placing him in the center of a very small set of people.[28,79–82]

For him to succeed with denial of involvement, he would need not only to be able to weather those questions and produce a plausible alternative path but he would also have needed to cover his tracks for the source of the material itself, as Dow reported that their inventory was still completely intact.[79,81,82] Despite that, in a *Psychedelic Salon* podcast, Scully commented that Shulgin provided a reference sample of 50 g to Stanley, along with an index card showing the basic steps for its synthesis.[41] The answer was very likely known only to Shulgin but in the course of digitizing his archives some possibilities emerged.

It would make sense if Shulgin wanted to rescue DOM from the state of pharmacological oblivion which would have been its certain fate had it never been published or developed further. He clearly valued the molecule, not only as his most powerful discovery to-date but the early accounts suggested to him that it held promise for therapeutic development.[8,21,42] His opinion was no doubt bolstered by the opinions expressed by other people including Snyder.[14,55] Even during the height of very first peak of the STP furor Shulgin opined to a researcher in Europe that "It would certainly be valuable to explore these active chemicals."[85]

Shelving DOM prior to its publication would not just stop further research and development by Dow; nothing more could be done with it in the future by Shulgin or by anyone else. Since nothing, not even its structure, had been published,[28] Shulgin could do nothing with DOM after leaving Dow, without outing himself. That would also be true if he were to have left Dow without there being a plausible route for the knowledge to have reached the public. It may be that the invitation on November 3, 1966, to present this material to the Pharmacology Department at Johns Hopkins in January 1967[74] provided inspiration for a route to expose the molecule. Without this opportunity arising, it would not have been possible to "safely" share the synthetic route with Stanley. It is reasonable to wonder whether Shulgin would have chosen to share the molecule without being provided with this potential cover story. In Tim Sculley's archives, comments from Stanley made it clear that Shulgin suggested Stanley should use this talk as the cover story for how he learned about DOM.[11,12]

During late 1966 to January of 1967, DOM must have been considered a valuable psychedelic drug and a potential pharmacological jewel in Shulgin's eyes, so its disappearance as a discontinued and unpublished drug could have been an unacceptable outcome. Shulgin made comments during his *Nature of Drugs* course concerning this

subject when discussing the role of strongly held beliefs in the context of differing or opposing positions on both sides of an equation, with opposing adherents each seeing themselves on the just side of a cause. He elaborated that this could enable people to engage in actions they might not otherwise without their sense of morality being compromised, due to the perception of the means being justified by the end.[88]

Shulgin also valued DOM highly as a molecule that could be of potential benefit for medical applications. This is quite evident in his Disclosures of Invention.[8,21] His opinion was shared by Snyder who was excited enough by the prospect that he commented in a letter to Dow's research director that "The euphoriant effect at doses which did not produce autonomic side-effects" (…) "possessed properties which may be of considerable use in clinical psychiatry." Snyder went on to speculate that he felt that both DOET and DOM might be found to have usefulness as therapeutics in clinical depression that did not respond to imipramine or amitriptyline.[55] This caught the attention of Dow sufficiently that they sent their research director to Baltimore to meet with Snyder and his associates on December 7, 1966, to discuss their proposed study of DOET.[62]

In 1967, Jack Jones, described as a Dow spokesperson, was quoted by a reporter "Preliminary tests have shown STP … can be a very valuable tool in the treatment of certain mental disorders" adding that it had appeared on the streets during the period of its early pharmacological investigation.[82] Dow told the New York Times that DOM was potentially useful in research on mental illness.[81] The potential for these molecules to help in understanding mental illness was at the core of Shulgin's research at Dow, driven by the then-prevalent hypothesis that methylation defects in catecholamine metabolism might be responsible for the appearance of schizophrenia and other mental and behavioral aberrations.[89–92] Shulgin's October 24, 1969, testimony to the House Select Committee on Crime in San Francisco indicated that research with molecules based on DOM continued at Dow after his departure.[93]

Interest in mental health applications of psychedelics had been the basis for his unpublished research papers at Dow concerning ring-substituted phenylisopropylamines.[21,94,95] This was also true for a paper submitted to Dow concerning chemotherapy of schizophrenia with DOM and DOET[48] and was reflected in the original title of the "one-ring psychotomimetics" paper submitted to *Nature* on September 13, 1968.[19,96] Shulgin had already vigorously published on compounds that were then referred to as having a psychotomimetic activity,[19,97–100] and during the 1969 congressional hearings in San Francisco, he again asserted that improvement of mental health was his research motivation.[93] Shulgin later obtained a use patent for the general structure shared by DOM, DOET and 1-(2,5-dimethoxy-4-methylphenyl)butan-2-amine, AKA dimoxamine, for increasing mental alertness and restoring performance in geriatric patients experiencing senility, depression, despondency, anxiety, Parkinsonism, or antisocial behavior.[101] Dimoxamine received IND status after licensing to Bristol-Meyers, and went through initial and Phase 2 clinical trials, but it was not developed further despite suggesting some promise in geriatrics and catatonics.[102] Recently, new patent applications have included DOM among compounds claimed to be capable of reducing inflammation; one suggested a utility for potential applications involving neuroplasticity[103] and another claiming "methods for reducing inflammation to improve or maintain mental health or physical health."[104]

A comment made about DOET in Snyder's proposed research protocols noted the interest of the Johns Hopkins group concerning its production of "a marked sense of well-being, almost euphoria." Snyder went on to propose that "… this psychotropic action might be useful in the clinical treatment of neurotic fatigue and depression," adding the psychedelic effects of higher dosage levels "might also be of utility as an adjunct to psychotherapy in some patients."[59] Snyder's personal experiences with DOET the next year supported his conviction of its value as a psychotherapeutic adjunct, but we have found no indications that he tried DOM personally.[105] If the reader is unfamiliar with this term, psychedelic drugs have been used as adjuncts to psychotherapy due to the resulting state of mind of the participant affording easier emotional access and less guarded content processing rather than the drug being given for having a direct therapeutic action. The most notable effects of DOET were described by Snyder as a mild euphoria with feelings of enhanced self-awareness lacking perceptual distortions or hallucinations.[65] Snyder's suggestion of potential uses offered some support for DOM itself in the subsequent work in humans at Johns Hopkins using 2.7 mg and 3.3 mg doses of DOM reporting a "significant reduction of depressive symptoms."[26] Double-blind testing established that a small dose of DOM also not only produced mild euphoria and enhanced self-awareness in humans without hallucinogenic effects but also "enhanced performance on serial learning tasks."[65]

These aspects of DOM are still dismissed by people whose familiarity is limited to the appearance of the street drug STP. Despite the public perception of STP as an "ugly, miserable, demonic two-to-three day non-trip for most people … High freak-out potential,"[23] that was not the same drug experience that was being proposed for use in psychiatric applications. The molecule was the same, but the dosage levels were quite different, as the street drug STP contained far more DOM than what Shulgin regarded to be an appropriate dose. This is a significant factor as the character of the intoxication changes as the dosage increases. At low dosage levels, the effect is as a mild euphoriant stimulant, and at higher levels, it becomes hallucinogenic. Snyder[65] and Hollister[15] provide more detailed descriptions of this phenomenon. Snyder suggested to Dow that there could be utility for both actions: lower doses for antidepressant activity and higher doses for use as a psychotherapeutic adjunct.[55] There is no question that Shulgin was familiar with the molecule having a psychedelic action or that he would have regarded this to be a positive aspect of the drug, and it is also clear that in January of 1967, he would have lacked personal familiarity with the results of any dosage above 4.9 mg.[106]

The highest dosage recorded in Shulgin's lab notebooks for any human[106] was less than half of the lowest dosage tableted by Stanley.[12] Tim Scully's archive[12] supports the accuracy of a myriad of popular accounts such as Meyers et al.[5] claiming that both 10 mg and 20 mg tablets were produced and distributed in 1967 after the first few tested at 30 mg were found to be "too strong."[11,12] However, we have located no account of any 20 mg tablets or 30 mg capsules ever

being tested by forensic chemists and finding its way into print. During that time period, the BDAC only reported analyzing tablets containing 9.1–10.2 mg.[37] Based on Shulgin's comments in correspondence with Snyder and others mentioned above, the 2–4 mg range appears to be what would have been used if it had continued into development. Shulgin's own experiences and the subjective experience descriptions of other evaluators had no doubt made an impression.[46] In the 4.1 mg experience of "W," the notes recorded by his observer included the comments: "Somewhat like mescaline," "Beautiful experience," "You MUST try it," "Like nothing else ever experienced," "Dynamic experience. Feels good too," "the CLOUDS!," "novel & pleasant," and so forth. An additional note reported the same subject later stated that compared to mescaline, peyote, and LSD "this ranks number 1."[46] Readers are reminded that these human experiments occurred in 1964, when LSD, peyote, and mescaline were not yet controlled substances, and DOM remained legal for another 4 years.[37,107] It is certain that Shulgin personally held DOM in high regard as a molecule with therapeutic value. In a 1983 conference presentation, he described his belief that each of the drugs he created represented "words" in a "vocabulary" of consciousness and of awareness that might help counterbalance our culture's drive towards annihilation. In this talk, he specifically mentioned "mescaline and psilocybin and DOM and LSD" as being "the widely publicized drugs of psychopharmacology" adding they had "played a role in defining the transition between drugs as entertainment … and drugs as instructive vehicles for learning, enlightenment and insight."[108,109]

He added, "It is here that I feel my skill lies and this is exactly why I do what I do."

7 | CHANGES IN THE LEGAL LANDSCAPE

Changes in federal legislation and the anticipation of more legal restrictions affecting the future of psychedelics research at Dow may also have been another motivation for Shulgin. The 1962 Kefauver-Harris Drug Amendments had imposed restrictions on drug research involving new molecules.[110] The Drug Abuse Control Amendment of 1965 added many restrictive elements for both drug producers and those engaged in pharmacological research.[111] Initial human evaluations at Dow were mentioned in scientific publications, so these legislative actions adversely affected the future of such work by Shulgin at Dow. In a March 6, 1966, letter to his coauthor Tony Sargent, Shulgin commented that their paper on MMDA was delayed by the Dow legal department as any molecule made at Dow entering a human would now be in violation of federal law.[112] He added their attorneys were not sure what to do; Shulgin proposed publishing as an independent researcher, as he had done previously in *Nature*. This appeared to settle the matter.

An internal Dow legal department communication of April 11, 1966, noted that an FDA inspector had visited on April 7, 1966, with a list of "hallucinatory drugs," to ask whether any were being produced at Dow. The visit was said to have lasted "no more than five minutes." The inspector had no other questions. Dow was not producing any of the listed chemicals. The inquiry was presented as an effort to prevent diversion of drugs from manufacturing facilities.[113] Dow likely realized pursuing this research was increasingly untenable. The restrictive effects of the new legislative environment may also have played a role in the favoring of DOET over DOM, as DOET was presented as not having a psychedelic action and being more euphoric than DOM.[14,114]

8 | THE PRODUCTION OF STP

In a conversation one of the authors (KT) had in 2004 with both Sand and Stanley, they related they had deliberately sought out Shulgin for advice, hoping for a suggestion about a drug that could replace LSD when it became illegal. It is not known exactly when Stanley asked Shulgin how to make DOM or requested a sample. Sand appears to have made the same request independently in correspondence around December 1, 1966.[115] In the Scully archives, he points out that when STP's memorable free distribution by Stanley occurred in 1967, Scully's DOM was not yet available.[12,84] Although Scully was already able to synthesize DOM and had done so, he was still perfecting the

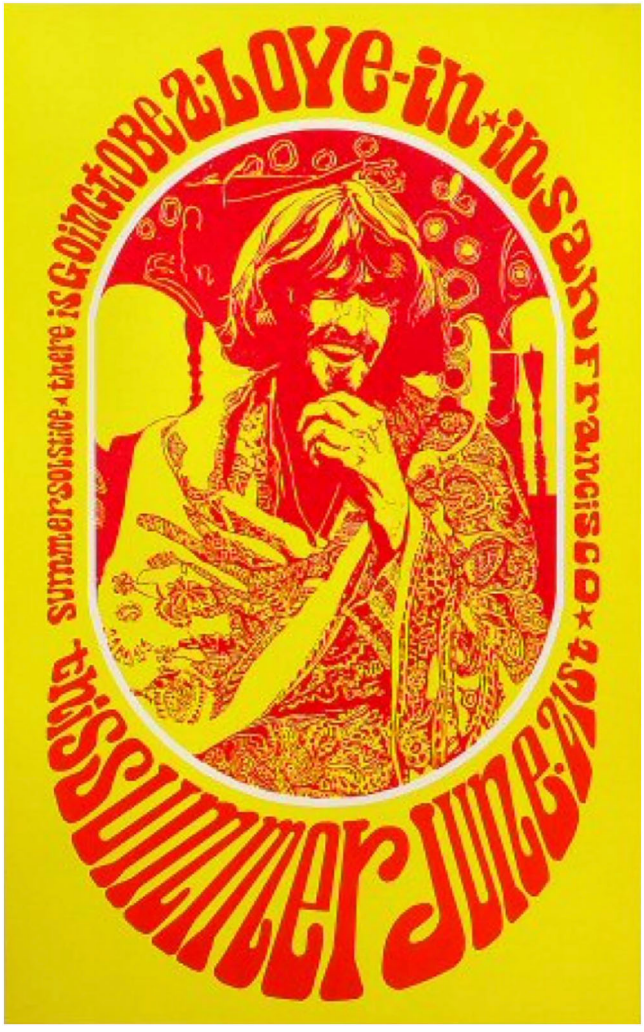

FIGURE 3 Love-in poster (1967).

final crystallization of its hydrochloride salt. This meant that the DOM produced in Denver was not yet ready for distribution to the public by Stanley and the material tableted and given away at the Summer Solstice Celebration "Love-In" in Golden Gate Park (Figure 3) had been made by Shulgin. The situation soon changed when Scully's material became available; Sand's production of STP also began shortly thereafter in 1967.[12]

9 | AFTERMATH

Though DOM has seldom been seen as a street drug since the early 1970s, it has contributed greatly to our understanding of basic neurochemistry and the neurophysiology of psychedelics. Shortly after its appearance as a street drug in the Summer of Love,[116] its pharmacology and neurological effects were probed in humans[15,96] and in animals.[117–119] Although DOM never saw a direct medical application, recent research has shown it to possess potent anti-inflammatory activity.[120] Mistaken warnings about chlorpromazine being contraindicated due to purportedly increasing the effects of DOM[121–123] lead to nonpharmacological interventions becoming a standard response of the medical community in instances of psychedelic emergencies.[83,124,125] DOM has been used extensively as a "standard reference" serotonergic hallucinogen starting in the late 1970s in rodent drug discrimination studies.[126–129] DOM helped elucidate the role of serotonin receptors in the action of hallucinogens[130–132] and the identification of the 5-HT_{2A} as a critical biological target.[133–136] It remains a valuable tool in the search for new psychedelics and in evaluating the receptor specificities of other compounds with therapeutic potential.[137,138]

10 | CONCLUSIONS

DOM appeared as a street drug for a short period of time, roughly 1967–1973. It similarly saw a brief period of interest by medical professionals but was never developed further. Those two paths of interest both originated with its inventor. There are still many unanswered questions that exist around formal pharmacological interest in DOM and it escaping into the public. We can only guess at motivations of the people involved beyond the few specific comments that exist in print from people like Shulgin, his coworkers, and Snyder. At the time, it was regarded by them to be a promising drug based on a limited number of human bioassays.

There are still many details that are not clear. It is evident is that the estimated size of the crowd that ingested "STP," at the summer solstice celebration on June 21, 1967, was inflated, as was the number of STP tablets reportedly being given to them. Replacing them with accurate numbers is simply not possible at this late date. The matter of the reported durations among drug users not being confirmed in clinical studies also remains unresolved. The extended durations reported in the press are not resolvable without more study in humans. Subsequent researchers were consistently unable to replicate similar outcomes in controlled studies. It may be that a person ingesting excessively large dosages might really experience a 3-day trip but other factors such as concurrent use of other drugs such as amphetamine or individual differences in metabolism cannot be ruled out. It may be that this question will never be adequately settled. Too much time has elapsed for memories to be reliable, and it is unlikely for any study to be approved in which humans would be monitored after ingesting 30 or more milligrams of DOM.

What appears to be clear from the available evidence is that the sample of DOM given to Stanley by Shulgin was the same material that was ingested in Golden Gate Park and created such a splash in the news. It is also certain that the Johns Hopkins presentation was employed by Shulgin as the cover story for how it had reached Stanley's awareness.

DOM appears to possibly have possessed some utility as a substance with potential use as a mild stimulant or as an anti-inflammatory, but it is extremely unlikely it could ever enjoy FDA authorized use in those areas due to the bad perceptions that linger due to its unauthorized appearance on the street and the wealth of bad press that was created in the process.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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