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Administrator.

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–568]

Schedules of Controlled Substances: Placement of Methoxetamine (MXE) in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration proposes placing 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one (methoxetamine, MXE), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation, in schedule I of the Controlled Substances Act. This action is being taken to enable the United States to meet its obligations under the 1971 Convention on Psychotropic Substances. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle, methoxetamine.

DATES: Comments must be submitted electronically or postmarked on or before February 7, 2022.

Interested persons may file a request for hearing or waiver of hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45 and/or 1316.47, as applicable. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing, together with a written statement of position on the matters of fact and law asserted in the hearing, must be received on or before January 6, 2022.

ADDRESSES: Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). The electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period. To ensure proper handling of comments, please reference ''Docket No. DEA–568'' on all electronic and written correspondence, including any attachments.

- *Electronic comments:* DEA encourages commenters to submit all comments electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to *https://www.regulations.gov* and follow the on-line instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number. Submitted comments are not instantaneously available for public view on *regulations.gov.* If you have received a Comment Tracking Number, you have submitted your comment successfully and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary and are discouraged. Should you wish to mail a paper comment in lieu of an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.
- *Hearing requests:* All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law asserted in the hearing, must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug & Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362–3249.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

All comments received in response to this docket are considered part of the public record. The Drug Enforcement Administration (DEA) will make comments available, unless reasonable cause is given, for public inspection online at *https://www.regulations.gov.* Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want DEA to make it publicly available, you must include the phrase ''PERSONAL IDENTIFYING INFORMATION'' in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want DEA to make it publicly available, you must include the phrase ''CONFIDENTIAL BUSINESS INFORMATION'' in the first paragraph of your comment. You must also

prominently identify the confidential business information to be redacted within the comment.

DEA will generally make available in publicly redacted form comments containing personal identifying information and confidential business information identified, as directed above. If a comment has so much confidential business information that DEA cannot effectively redact it, DEA may not make available publicly all or part of that comment. Comments posted to *https://www.regulations.gov* may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as confidential as directed above.

An electronic copy of this document and supplemental information to this proposed rule are available at *https://www.regulations.gov* for easy reference.

Request for Hearing or Appearance; Waiver

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking ''on the record after opportunity for a hearing.'' Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act, 5 U.S.C. 551–559. 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D. Interested persons may file requests for a hearing or notices of intent to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(a) or (b), and such requests must include a statement of interest in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. 21 CFR 1316.47(a). Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person's position on the matters of fact and law involved in any hearing as set forth in 21 CFR 1308.44(c).

All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information provided above.

Legal Authority

The United States is a party to the 1971 United Nations Convention on Psychotropic Substances (''1971 Convention''), February 21, 1971, 32 U.S.T. 543, 1019 U.N.T.S. 175, as amended. Procedures respecting changes in drug schedules under the 1971 Convention are governed domestically by 21 U.S.C. 811(d)(2)–(4). When the United States receives notification of a scheduling decision pursuant to Article 2 of the 1971 Convention indicating that a drug or other substance has been added to a schedule specified in the notification, the Secretary of the Department Health and Human Services (HHS),[1] after consultation with the Attorney General, shall first determine whether existing legal controls under subchapter I of the Controlled Substances Act (CSA) and the Federal Food, Drug, and Cosmetic Act meet the requirements of the schedule specified in the notification with respect to the specific drug or substance. 21 U.S.C. 811(d)(3). In the event that the Secretary of HHS (Secretary) did not consult with the Attorney General, and the Attorney General did not issue a temporary order, as provided under 21 U.S.C. 811(d)(4), the procedures for permanent scheduling set forth in 21 U.S.C. 811(a) and (b) control. Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may add to such a schedule any drug or other substance, if he finds that such drug or other substance has a potential for abuse, and makes the findings prescribed by 21 U.S.C. 812(b) for the schedule in which such drug or other substance is to be placed. The Attorney General has delegated this scheduling authority to the Administrator of DEA. 28 CFR 0.100.

Background

Methoxetamine (MXE), also known as 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one or 2-(3-methoxyphenyl)-2-(*N*-ethylamino)cyclohexanone belongs to the arylcyclohexylamine class of drugs with dissociative anesthetic and hallucinogenic properties, similar to phencyclidine (PCP) and ketamine. Methoxetamine has no approved medical use in the United States.

On December 30, 2014, DEA, in accordance with the provisions of 21 U.S.C. 811(b), requested HHS provide a scientific and medical evaluation as well as a scheduling recommendation for methoxetamine. On April 14, 2017, DEA provided HHS additional scientific and updated information on methoxetamine. The April 14, 2017, communication included that on May 17, 2016, the Secretary-General of the United Nations (UN Secretary General) advised the Secretary of State of the United States that the Commission on Narcotic Drugs (CND), during its 59th Session in March 2016, voted to place methoxetamine in Schedule II of the 1971 Convention (CND Dec/59/6). As a signatory to this international treaty, the United States is required, by scheduling under the CSA, to place appropriate controls on methoxetamine to meet the minimum requirements of the treaty.

Article 2, paragraph 7(b), of the 1971 Convention sets forth the minimum requirements that the United States must meet when a substance has been added to Schedule II of the 1971 Convention. Pursuant to the 1971 Convention, the United States must require licenses for the manufacture, export and import, and distribution of methoxetamine. This license requirement is accomplished by the CSA with the registration requirement as set forth in 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. In addition, the United States must adhere to specific export and import provisions that are provided in the 1971 Convention. This requirement is accomplished by the CSA with the export and import provisions established in 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312. Likewise, under Article 13, paragraphs 1 and 2, of the 1971 Convention, a party to the 1971 Convention may notify another party, through the UN Secretary-General, that it prohibits the importation of a substance in Schedule II, III, or IV of the 1971 Convention. If such notice is presented to the United States, the United States shall take measures to ensure that the named substance is not exported to the country of the notifying party. This requirement is also accomplished by the export provisions of the CSA mentioned above. Under Article 16, paragraph 4, of the 1971 Convention, the United States is required to provide annual statistical reports to the International Narcotics Control Board (INCB). Using INCB Form P, the United States shall provide the following information: (1) In regard to each substance in Schedule I and II of the 1971 Convention, quantities manufactured, exported to and imported from each country or region as well as stocks held by manufacturers; (2) in regard to each substance in Schedule III and IV of the 1971 Convention, quantities manufactured, as well as quantities exported and imported; (3) in regard to each substance in Schedule II

[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 Controlled Substances Act, with the concurrence of NIDA. 50 FR 9518 (March 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).

and III of the 1971 Convention, quantities used in the manufacture of exempt preparations; and (4) in regard to each substance in Schedule II–IV of the 1971 Convention, quantities used for the manufacture of non-psychotropic substances or products. Lastly, under Article 2 of the 1971 Convention, the United States must adopt measures in accordance with Article 22 to address violations of any statutes or regulations that are adopted pursuant to its obligations under the 1971 Convention. The United States complies with this provision as persons acting outside the legal framework established by the CSA are subject to administrative, civil, and/or criminal action.

DEA notes that there are differences between the schedules of substances in the 1971 Convention and the CSA. The CSA has five schedules (schedules I–V) with specific criteria set forth for each schedule. Schedule I is the only possible schedule in which a drug or other substance may be placed if it has high potential for abuse and no currently accepted medical use in treatment in the United States. See 21 U.S.C. 812(b). In contrast, the 1971 Convention has four schedules (Schedules I–IV) but does not have specific criteria for each schedule. The 1971 Convention simply defines its four schedules, in Article 1, to mean the correspondingly numbered lists of psychotropic substances annexed to the Convention, and altered in accordance with Article 2.

Proposed Determination To Schedule Methoxetamine

Pursuant to 21 U.S.C. 811(b), DEA gathered the necessary data on methoxetamine and on December 30, 2014, submitted it to the Acting Assistant Secretary for Health of HHS (Acting Assistant Secretary) with a request for a scientific and medical evaluation of available information and a scheduling recommendation for methoxetamine. Subsequently, on April 14, 2017, DEA submitted additional data on methoxetamine to the Acting Assistant Secretary. On April 14, 2018, HHS provided to DEA a scientific and medical evaluation entitled ''Basis for the Recommendation to Place (2-(3-methoxyphenyl)-2-(*N*-ethylamino)-cyclohexanone) Methoxetamine and its Optical Isomers and Salts in Schedule I of the Controlled Substances Act'' and a scheduling recommendation. Following consideration of the eight factors and findings related to the substance's abuse potential, legitimate medical use, and dependence liability, HHS recommended that methoxetamine and its optical isomers and salts be controlled in schedule I of the CSA under 21 U.S.C. 812(b). In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS and all other relevant data, and completed its own eight-factor review pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by HHS and DEA in their respective eight-factor analyses, and as considered by DEA in this proposed scheduling determination. Please note that both DEA and HHS analyses are available in their entirety under ''Supporting Documents'' of the public docket for this proposed rule at *https://www.regulations.gov* under docket number ''DEA–568.''

1. The Drug's Actual or Relative Potential for Abuse

In addition to considering the information HHS provided in its scientific and medical evaluation document for methoxetamine, DEA also considered all other relevant data regarding actual or relative potential for abuse of methoxetamine. 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: [2]

a. 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

b. There is a significant diversion of the drug or other substance from legitimate drug channels; or

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

d. The drug is so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions 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.

DEA reviewed the scientific and medical evaluation provided by HHS and all other data relevant to the abuse potential of methoxetamine. These data as presented below demonstrate that methoxetamine has a high potential for abuse.

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

According to HHS, individuals are taking methoxetamine in amounts sufficient to create a hazard to their health or to the safety of other individuals and to the community. Published case reports described non-fatal and fatal intoxications from the United States and Europe, including Poland, the United Kingdom, and Switzerland. The 2014 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) report on methoxetamine mentioned 20 confirmed (by analysis of postmortem biological samples) death reports received between 2011 and 2013 from European Union Member States to the Early Warning System. Between 2011 and 2014, scientific publications have reported one death related to methoxetamine from Switzerland, eight deaths from the United Kingdom, and at least two deaths from Poland. In the United States, methoxetamine has been reported as the cause of death in two cases; one case was mentioned in the 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System, and the second case was from a 2013 news report mentioning the Medical Examiner's findings from that death. Additionally, two case reports suggest that some individuals use methoxetamine to self-medicate for some clinical conditions, specifically chronic foot pain and post-traumatic stress disorder. Further, a case report published in 2019 suggests a single injection of methoxetamine can induce prolonged psychosis with confirmed cognitive deficits. As stated by HHS, when abused, methoxetamine can be administered through intranasal (insufflation or snorting), oral, sublingual, rectal, intramuscular, and intravenous routes of administration. Abuse of methoxetamine, similar to PCP and ketamine abuse, produces dissociative anesthetic and hallucinogenic effects, including somatic and psychological effects such as: Euphoria, increased empathy, sense of dissociation from the body, vivid visual hallucinations, and pleasant intensification of sensory experiences. Users report in online forums that methoxetamine generally produces longer lasting effects, with a delayed

[2] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91–1444, 91st Cong., 2nd Sess. (1970) reprinted in 1970 U.S.C.C.A.N. 4566, 4603.

onset compared to PCP or ketamine. At higher doses (>40 mg), users describe the experience as reaching the ''m-hole,'' which is similar to the ketamine ''k-hole'' experience and characterized by extreme dissociation from the body, comparable to an out-of-body experience.

HHS reports that commonly reported side effects of methoxetamine include dizziness, confusion, time distortion, aphasia, psychomotor agitation, vertigo, incoordination, nausea, and vomiting. Similar to PCP and ketamine toxicity, signs and symptoms (toxidrome) of methoxetamine toxicity can be grouped into three types: Dissociative/delirious, sympathomimetic, and cerebellar symptoms. Dissociative or delirious symptoms include depersonalization, derealization, catatonia, audiovisual hallucinations, delusions, confusion, altered or loss of consciousness, agitation, aggression, amnesia, and mood lability. Sympathomimetic symptoms include rapid heart rate (tachycardia), high blood pressure (hypertension), elevated body temperature (pyrexia), rapid breathing (tachypnea), and pupillary dilation (mydriasis). Cerebellar symptoms include inability to sit (truncal ataxia), incoordination, speech impairment (dysarthria), impaired ability to perform rapid alternating movements (dysdiadochokinesis), and rapid and repetitive uncontrolled eye movements (nystagmus). Summarized withdrawal symptoms reported on online forums include low mood, depressive thoughts, and cognitive impairment for many hours in one user followed by two days of insomnia after a single 100 mg intranasal administration. One user reported a suicide attempt after discontinued use of methoxetamine.

HHS states that treatment of acute toxicity caused by methoxetamine and other drugs of the same class (*e.g.,* PCP and ketamine) consists of supportive treatment to control or relieve psychological complications and side effects. This treatment may include administration of benzodiazepines, antiemetics, intravenous fluids, and respiratory support, if needed.

DEA notes that ketamine has been known to cause toxicities to the bladder and renal system. When mice were given daily dose of 30 mg/kg methoxetamine intraperitoneally (i.p.) for 90 days, significant bladder and renal toxicity occurred. Thus, like ketamine, chronic administration of methoxetamine is associated with bladder and renal toxicity, including inflammatory changes with subsequent fibrosis that could lead to bladder and kidney damage.

b. There is Significant Diversion of the Drug or Substance From Legitimate Drug Channels

HHS states that methoxetamine is not a Food and Drug Administration (FDA)-approved drug product for treatment in the United States and is unaware of any country in which its use is legal. There appear to be no legitimate sources for methoxetamine as a marketed drug. Thus, there is no evidence of significant diversion of methoxetamine from legitimate drug channels.

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

Methoxetamine is not approved for medical use and is not formulated or available for clinical use. Therefore, it is assumed that individuals are taking methoxetamine on their own initiative, rather than based on medical advice from a properly-licensed practitioner. This is consistent with the data from law enforcement seizures and case reports indicating that individuals are taking methoxetamine on their own initiative rather than on the medical advice of a licensed practitioner.

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

Methoxetamine is a synthetic arylcyclohexylamine and has pharmacological properties similar to other arylcyclohexylamines such as the ethylamine analog of phencyclidine (PCE; schedule I), the thiophene analog of phencyclidine (TCP; schedule I), phencyclidine (PCP, schedule II), and ketamine (schedule III). Methoxetamine, similar to PCE, TCP, PCP, and ketamine, has been shown to produce dissociative anesthetic and hallucinogenic effects.

As mentioned in HHS' review, the primary mechanism of action of methoxetamine is thought to be on glutamatergic neurotransmission. Glutamate is the major excitatory neurotransmitter system in the brain. *In vitro* binding studies show that methoxetamine binds to the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor and acts as an antagonist with similar potency as PCP and ketamine. HHS notes that, similar to PCP, methoxetamine also has affinity for the serotonin reuptake transporter and acts as a serotonin reuptake inhibitor. Further, like many drugs of abuse, methoxetamine acutely increases the firing rate and bursting activity of ventral tegmental area (VTA) dopaminergic neurons projecting to the nucleus accumbens (NAc), and inhibits the reuptake of dopamine. The VTA is an area of the brain, rich in dopamine and serotonin neurons, which along with the NAc is part of the brain reward pathway. The increase in the firing rate and bursting activity of dopamine neurons produced by PCP, ketamine, and methoxetamine that results in increased dopamine levels in the VTA may underlie the psychotomimetic and reinforcing properties of these drugs.

Drug discrimination (an *in vivo* test to assess drug abuse liability and compare drugs to known drugs of abuse) data demonstrate that methoxetamine, similar to PCP, fully substitutes for the discriminative stimulus effect of ketamine in rats. Additionally, conditioned place preference (CPP) studies and self-administration studies used to assess rewarding and reinforcing effects show that methoxetamine produces both rewarding and reinforcing effects. Taken together, methoxetamine produces psychopharmacological effects similar to those produced by ketamine and PCP in animal models that are predictive of abuse potential in humans.

As stated by HHS, users of methoxetamine experience effects similar to those of ketamine and PCP including depersonalization, a mild to strong sense of dissociation from the physical body, distortion of the sense of reality, and vivid visual hallucinations. More negative or challenging effects of methoxetamine, similar to PCP and ketamine, may also occur and include delusions, tachycardia, hypertension, agitation, aggression, and cerebellar toxicity. Case reports of overdose and deaths resulting from methoxetamine abuse have been reported between 2011 and 2019 in scientific literature and by international authorities.

As mentioned by HHS, methoxetamine is being abused for its psychoactive effects. DEA further notes that based on concerns related to trafficking and availability, as well as the risks to the public health associated with its abuse, at least ten states in the United States have controlled methoxetamine. At the international level, as of June 2020, methoxetamine has been controlled in Russia,

Switzerland, Israel, Sweden, United Kingdom, Japan, Germany, France, Brazil, China, Poland, and the European Union member states.

2. Scientific Evidence of the Drug's Pharmacological Effects, if Known

Methoxetamine is an antagonist at the glutamatergic NMDA receptors (with moderately high affinity) and a reuptake inhibitor at the serotonin transporter. Acute methoxetamine exposure increases the firing rate and bursting activity of the ventral tegmental area (VTA) dopaminergic neurons projecting to the nucleus accumbens (NAc) and inhibits reuptake of dopamine, similarly to PCP and ketamine. The VTA is an area of the brain that is rich in dopamine and serotonin neurons and is a contributing part of the brain reward pathway, as is the NAc. The net result is an increase in dopamine levels in the VTA, which may underlie the psychomimetic and reinforcing effects of these drugs.

Animal testing data in rats show that methoxetamine, like PCP, fully substitutes for ketamine discriminative stimulus. Additionally, rats self-administer methoxetamine. Data from self-administration and CPP studies show that methoxetamine has rewarding and reinforcing effects. Thus, methoxetamine produces psychopharmacologic effects similar to those produced by other NMDA antagonists (PCP and ketamine) in animal models, which are predictive of its abuse in humans.

In humans, users of methoxetamine report dissociative anesthetic and hallucinogenic effects similar to PCP and ketamine including euphoria, increased empathy, dissociation from the body, vivid visual hallucinations, and pleasant intensification of sensory experiences. Delusion, tachycardia, hypertension, agitation, aggression, and cerebellar toxicity have also been reported. Methoxetamine-associated overdose and deaths have been reported in scientific literature and by international authorities between 2011 and 2019.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

Chemistry

Methoxetamine, also known as also known as MXE, 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one, or 2-(3-methoxyphenyl)-2-(*N*-ethylamino)cyclohexanone, has a molecular weight of 247.338 g/mol. Methoxetamine is primarily present as a white crystalline powder and has also been reported as being off-white, beige, or yellow in color. The Chemical Abstract Service Registry Numbers for methoxetamine are 1239943–76–0 for methoxetamine base and 1239908–48–5 for methoxetamine as the hydrochloride salt. Its molecular formula (as base) is $C_{15}H_{21}NO_2$. Methoxetamine hydrochloride (salt) is soluble in organic solvents like ethanol (10 mg/mL) at 25 °C, dimethyl sulfoxide (DMSO) (14 mg/mL), and dimethyl formamide (5 mg/mL). It is also soluble in aqueous solvents like a pH 7.2 phosphate buffer (5 mg/mL). Synthesis and characterization of methoxetamine and analytical data (nuclear magnetic resonance spectroscopy, mass spectroscopy, and infrared spectroscopy) are reported in the scientific literature.

Pharmacokinetics and Toxicology

Controlled pharmacokinetic clinical research studies have not been conducted to characterize the onset of action, the plasma concentrations after ingestion of a fixed dose of methoxetamine, or to determine the half-life of methoxetamine. However, since methoxetamine has been used recreationally, a summary and description of the onset and duration of the effects of methoxetamine that come from user reports, generally via online forums, can be found in the scientific literature.

A summary of online user reports suggests that methoxetamine is generally administered through intranasal (insufflation or snorting), oral, sublingual, rectal, and intramuscular routes with additional reports of intravenous use. Dose range administered, onset of drug effects, and duration of drug effects vary by the route of administration. Dose associated with intranasal use is 20 to 60 mg, oral administration is 20 to 100 mg, and intramuscular administration is 10 to 50 mg, with reported onset of drug effects of 30 to 90 minutes following intranasal use, up to 90 minutes following oral administration, and five minutes following intramuscular administration. Drug effects can last 2.5 to 7 hours following nasal use, 3 to 5 hours following oral ingestion, and 1 to 4 hours after intramuscular injection. Typical doses and drug-related time effects were not reported for other routes of administration.

As HHS reports, the metabolism of methoxetamine was investigated using human liver microsomes *in vitro* and compared to toxicological analysis of urine from individuals presenting with analytically confirmed acute methoxetamine toxicity. Liquid chromatography high-resolution mass spectrometry was used to identify and characterize the metabolites of methoxetamine *in vitro* and *in vivo.* These studies reported complex metabolism of methoxetamine including *N*-deethylation, *O*-demethylation, hydroxylation, reduction, and dehydrogenation followed by glucuronization (conjugation of the metabolites with glucuronic acid). The normethoxytamine (desethylmethoxetamine) is the main metabolite identified in both *in vivo* and *in vitro* studies.

HHS further states that kinetic studies with human hepatic CYP isozymes have showed that *N*-deethylation is catalyzed by CYP2B6 and CYP3A4, *O*-demethylation by CYP2B6 and CYP2C19, and hydroxylation by CYP2B6. These studies also showed that normethoxamine is the major metabolite in humans and rats.

The role of CYP2B6 in methoxetamine metabolism is of particular importance. Because CYP2B6 is involved in metabolism of numerous drugs (*e.g.,* bupropion, methadone, propofol, sertraline), pharmacokinetic interactions between methoxetamine and other compounds are likely to occur. In addition, the rate of methoxetamine metabolism and toxicity may depend on genetic polymorphism of CYP2B6. Currently, it is unknown if any specific methoxetamine metabolites are biologically active.

4. Its History and Current Pattern of Abuse

As HHS notes, methoxetamine, similar to ketamine and PCP, is a synthetic arylcyclohexylamine with dissociative anesthetic properties. Typical routes of administration by drug users include oral, nasal insufflation, intramuscular, rectal, and intravenous. Based on available abuse data, public health risk, and drug trafficking data, the World Health Organization (WHO) recommended to the United Nations that methoxetamine be controlled internationally. In March 2016, the CND voted to place methoxetamine in Schedule II of the 1971 Convention.

In 2014, WHO reported that methoxetamine has been available in Europe since 2010. Distribution and trafficking of methoxetamine occurred largely via the internet. According to the law enforcement data, the first encounter in the United States occurred in mid-2011.

In 2015, WHO reported non-fatal intoxications and more than 20 deaths associated with methoxetamine. Since 2014 through 2019, there have been reports of several other overdoses and

deaths in which methoxetamine was implicated in Europe. In the United States, there have been at least two documented deaths associated with the use of methoxetamine, one occurring in 2012 and the other in 2014.

5. The Scope, Duration, and Significance of Abuse

In the United States, evidence of abuse of methoxetamine initially appeared in mid-2011 when a case study was published regarding an individual who was brought to the emergency department following methoxetamine intoxication in Massachusetts. The first reported death in the United States from methoxetamine abuse occurred in Milwaukee County, Wisconsin, in May 2012.

Data from the System to Retrieve Information on Drug Evidence (STRIDE) and STARLiMS [3] and the National Forensic Laboratory Information System (NFLIS) [4] indicate that methoxetamine was found in samples starting in August 2004, in California. Specifically, there were 114 STRIDE/STARLIMS reports from August 2004 through July 2021, and 677 NFLIS reports from January 2011 to July 2021. Combining drug reports and exhibits from both NFLIS and STRIDE between August 2004 and July 2021, methoxetamine has been encountered in 45 states and the District of Columbia. Methoxetamine drug quantities seized by United States Customs and Border Protection (CBP) have ranged from 2 to 200 grams. Reportedly, a small percentage of the methoxetamine reports from CBP were in combination with other drugs, such as synthetic cannabinoids, synthetic cathinones, ketamine, caffeine, and sildenafil.

In response to abuse and safety concerns, methoxetamine has been controlled in Virginia, Minnesota, North Dakota, Florida, Ohio, Indiana, Louisiana, Alabama, Arizona, and Utah.

Abuse of methoxetamine has been characterized as causing acute public health and safety issues worldwide. Methoxetamine is now controlled in Russia, Switzerland, Israel, Sweden, United Kingdom, Japan, Germany, France, Brazil, China, Poland and the European Union member states. On September 25, 2014, the European Union council decided to control methoxetamine in all European member states, and on March 18, 2016, the CND, at its 59th Session, added methoxetamine to Schedule II of the 1971 Convention.

6. What, if Any, Risk There Is to the Public Health

Methoxetamine shares similar mechanisms of action with and produces similar physiological and subjective effects (see Factor 2 for more information) as other controlled arylcyclohexylamines, such as the ethylamine analog of phencyclidine (PCE; schedule I), the thiophene analog of phencyclidine (TCP; schedule I), phencyclidine (PCP; schedule II), and ketamine (schedule III). Thus, methoxetamine poses the same risks to public health as PCE, TCP, PCP, and ketamine. Predominantly, the risks to public health are centralized to risks of the user, but in some cases do affect the general public, as is the case of driving under the influence.

Users of methoxetamine describe the drug effects as being similar to those of PCP and ketamine. Effects often include hallucinations and dissociation of the physical body, and can produce antidepressant-like effects. Online reports of use of methoxetamine suggest it is used via all routes of administration (*i.e.,* intranasal, oral, intramuscular, rectal, and intravenous). Due to the various routes of administration, the onset of effects can vary widely (one minute for intravenous to 90 minutes intranasal).

As HHS notes, several case reports pertaining to methoxetamine use, toxicities, and fatal intoxications have been published in the scientific and medical literature in several countries. In particular, in 2014 EMCDDA reported that methoxetamine was mentioned in 20 biologically confirmed death reports from the European Union member states Early Warning System. At least one published death related to methoxetamine has occurred in Switzerland, eight deaths in the United Kingdom, two deaths in Poland, and two deaths in the United States. In 2015, WHO indicated that a total of 120 nonfatal intoxications and 22 deaths related to methoxetamine had been reported, in which many but not all had been biologically confirmed. Two case reports suggest some individuals use methoxetamine to self-medicate to treat various clinical conditions, specifically chronic foot pain and post-traumatic stress disorder. In addition, DEA further notes one case report published in 2019 suggests methoxetamine can induce prolonged psychosis after a single injection.

7. Its Psychic or Physiological Dependence Liability

Psychological and physiological dependence are associated with methoxetamine. The euphoric and hallucinogenic effects associated with methoxetamine and other arylcyclohexylamine drugs serve as reinforcers and can result in psychological dependence and are supported by case studies with methoxetamine abusers. Several preclinical studies and case reports examined and described physical dependence and withdrawal effects associated with methoxetamine abuse. Signs of methoxetamine withdrawal have included low mood and/or depressive thoughts, cognitive impairment lasting several hours followed by two days of insomnia after last use, and a reported suicide attempt.

8. Whether the Substance Is an Immediate Precursor of a Substance Already Controlled Under the CSA

DEA and HHS find that methoxetamine is not an immediate precursor of any controlled substance of the CSA.

Conclusion

Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and on DEA's consideration of its own eight-factor analysis, DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of methoxetamine. As such, DEA hereby proposes to schedule methoxetamine as a controlled substance under the CSA.

Proposed Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V. The CSA also outlines the findings required to place a drug or other substance in any particular schedule, 21 U.S.C. 812(b). After consideration of the analysis and recommendation of the Acting Assistant Secretary for Health of HHS and review of all other available data, the Administrator of DEA, pursuant to 21 U.S.C. 812(b)(1), finds that:

(1) Methoxetamine has a high potential for abuse that is comparable to other scheduled substances such as the ethylamine analog of phencyclidine (PCE; schedule I), the thiophene analog

[3] STARLiMS is a web-based, commercial laboratory information management system that systematically collects results from drug chemistry analyses conducted by DEA laboratories. On October 1, 2014, STARLiMS replaced STRIDE as DEA's laboratory drug evidence data system of record. DEA laboratory data submitted after September 30, 2014 are reposited in STARLiMS. STRIDE/STARLiMS data were queried on August 18, 2021.

[4] NFLIS is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by state and local forensic laboratories in the United States. NFLIS data were queried on August 18, 2021.

of phencyclidine (TCP; schedule I), phencyclidine (PCP; schedule II), and ketamine (schedule III);

(2) Methoxetamine has no currently accepted medical use in treatment in the United States. There are no approved New Drug Applications for methoxetamine and no known therapeutic applications for methoxetamine in the United States. Therefore, methoxetamine has no currently accepted medical use in treatment in the United States.[5]

(3) There is a lack of accepted safety for use of methoxetamine under medical supervision. Because methoxetamine has no approved medical use and has not been investigated as a new drug, its safety for use under medical supervision has not been determined. Therefore, there is a lack of accepted safety for use of methoxetamine under medical supervision.

Based on these findings, the Acting Administrator of DEA concludes that methoxetamine warrants control in schedule I of the CSA. More precisely, because of its hallucinogenic effects, and because it may produce hallucinogenic-like tolerance and dependence in humans, DEA proposes to placing methoxetamine, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical description, in 21 CFR 1308.11(d) (the hallucinogenic substances category of schedule I).

Requirements for Handling Methoxetamine

If this rule is finalized as proposed, methoxetamine would be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, import, export, engagement in research, conduct instructional activities or chemical analysis with, and possession of schedule I controlled substances, including the following:

1. Registration. Any person who handles (manufactures, distributes, reverse distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses), or who desires to handle, methoxetamine would be required to be registered with DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312, as of the effective date of a final scheduling action. Any person who currently handles methoxetamine and is not registered with DEA would need to submit an application for registration and may not continue to handle methoxetamine as of the effective date of a final scheduling action, unless DEA has approved that application for registration pursuant to 21 U.S.C. 822, 823, 957, 958, and in accordance with 21 CFR parts 1301 and 1312.

2. Disposal of stocks. Any person who does not desire or is not able to obtain a schedule I registration would be required to surrender or transfer all quantities of currently held methoxetamine to a person registered with DEA before the effective date of a final scheduling action in accordance with all applicable Federal, State, local, and tribal laws. As of the effective date of a final scheduling action, methoxetamine would be required to be disposed of in accordance with 21 CFR part 1317, in addition to all other applicable Federal, State, local, and tribal laws.

3. Security. Methoxetamine would be subject to schedule I security requirements and would need to be handled and stored pursuant to 21 U.S.C. 823, and in accordance with 21 CFR 1301.71–1301.93, as of the effective date of a final scheduling action. Non-practitioners handling methoxetamine would also need to comply with the employee screening requirements of 21 CFR 1301.90–1301.93.

4. Labeling and Packaging. All labels, labeling, and packaging for commercial containers of methoxetamine would need to be in compliance with 21 U.S.C. 825, and be in accordance with 21 CFR part 1302, as of the effective date of a final scheduling action.

5. Quota. Only registered manufacturers would be permitted to manufacture methoxetamine in accordance with a quota assigned pursuant to 21 U.S.C. 826, and in accordance with 21 CFR part 1303, as of the effective date of a final scheduling action.

6. Inventory. Every DEA registrant who possesses any quantity of methoxetamine on the effective date of the final scheduling action would be required to take an inventory of methoxetamine on hand at that time, pursuant to 21 U.S.C. 827, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (d).

Any person who becomes registered with DEA on or after the effective date of the final scheduling action would be required to take an initial inventory of all stocks of controlled substances (including methoxetamine) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827 and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (b).

After the initial inventory, every DEA registrant would be required to take a new inventory of all controlled substances (including methoxetamine) on hand every two years, pursuant to 21 U.S.C. 827 and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

7. Records and Reports. Every DEA registrant would be required to maintain records and submit reports for methoxetamine, or products containing methoxetamine, pursuant to 21 U.S.C. 827 and in accordance with 21 CFR 1301.74(b) and (c) and parts 1304, 1312, and 1317, as of the effective date of a final scheduling action. Manufacturers and distributors would need to submit reports regarding methoxetamine to the Automation of Reports and Consolidated Order System pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304 and 1312, as of the effective date of a final scheduling action.

8. Order Forms. Every DEA registrant who distributes methoxetamine would be required to comply with the order form requirements, pursuant to 21 U.S.C. 828, and 21 CFR part 1305, as of the effective date of a final scheduling action.

9. Importation and Exportation. All importation and exportation of methoxetamine would need to be in compliance with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312, as of the effective date of a final scheduling action.

10. Liability. Any activity involving methoxetamine not authorized by, or in violation of, the CSA or its implementing regulations, would be unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

[5] Although there is no evidence suggesting that methoxetamine has a currently accepted medical use in treatment in the United States, it bears noting that a drug cannot be found to have such medical use unless DEA concludes that it satisfies a five-part test. Specifically, with respect to a drug that has not been approved by the FDA, to have a currently accepted medical use in treatment in the United States, all of the following must be demonstrated:

i. The drug's chemistry must be known and reproducible;

ii. there must be adequate safety studies;

iii. there must be adequate and well-controlled studies proving efficacy;

iv. the drug must be accepted by qualified experts; and

v. the scientific evidence must be widely available.

57 FR 10499 (1992), *pet. for rev. denied, Alliance for Cannabis Therapeutics* v. *DEA,* 15 F.3d 1131, 1135 (D.C. Cir. 1994).

Regulatory Analyses

Executive Orders 12866 and 13563, Regulatory Planning and Review, Improving Regulation and Regulatory Review

In accordance with 21 U.S.C. 811(a), this proposed scheduling action is subject to formal rulemaking procedures performed ''on the record after opportunity for a hearing,'' which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

Executive Order 12988, Civil Justice Reform

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This proposed rulemaking does not have federalism implications warranting the application of E.O. 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This proposed rule does not have tribal implications warranting the application of E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Paperwork Reduction Act of 1995

This proposed action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521).

Regulatory Flexibility Act

The Acting Administrator of DEA, in accordance with the Regulatory Flexibility Act, 5 U.S.C. 601–612, has reviewed this proposed rule, and by approving it, certifies that it will not have a significant economic impact on a substantial number of small entities.

DEA proposes placing the substance methoxetamine (chemical name: 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation, in schedule I of the CSA. This action is being taken to enable the United States to meet its obligations under the 1971 Convention. If finalized, this action would impose the regulatory controls and administrative, civil, and/or criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess) or propose to handle methoxetamine.

According to HHS, and also per DEA's findings in this proposed rule, methoxetamine has high potential for abuse, has no currently accepted medical use in treatment in the United States, and lacks accepted safety for use under medical supervision. DEA's research confirms that there is no commercial market for methoxetamine in the United States. As such, the proposed rule will not have a significant effect on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the ''Regulatory Flexibility Act'' section above, DEA has determined pursuant to the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 *et seq.*) that this proposed action would not result in any Federal mandate that may result ''in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year * * *.'' Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is proposed to be amended as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

■ 1. The authority citation for 21 CFR part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

■ 2. In § 1308.11, as proposed to be amended at 86 FR 16553 (March 30, 2021) and 86 FR 37719 (July 16, 2021), add paragraph (d)(100) to read as follows:

§ 1308.11 Schedule I.

* * * * *

(d) * * *

(100) 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one (methoxetamine, MXE)	7286

* * * * *

Anne Milgram,

Administrator.

[FR Doc. 2021–26293 Filed 12–6–21; 8:45 am]

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