



Billing Code 4410-09-P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-498]

Schedules of Controlled Substances: Placement of 4,4'-DMAR in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration proposes placing the substance 4,4'-DMAR (Chemical name: 4,4'-dimethylaminorex), including its salts, isomers, and salts of isomers, 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 4,4'-DMAR.

DATES: Comments must be submitted electronically or postmarked on or before [INSERT DATE 60 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

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 must be received on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). Commenters should be aware that 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-498” on all electronic and written correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the webpage or attach a file for lengthier comments. Please go to <http://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 for your comment. Please be aware that submitted comments are not instantaneously available for public view on regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted 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 Morrisette Drive, Springfield, Virginia 22152.

- *Hearing requests:* All requests for a hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrisette 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 Morrisette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrisette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received in response to this docket are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at <http://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 (FOIA) 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 it to be made 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 it to be made 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.

Comments containing personal identifying information and confidential business information identified, as directed above, will generally be made publicly available in redacted form. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to *http://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 directed above as confidential.

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

Request for Hearing or Waiver of Participation in Hearing

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 (APA), 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 include a statement of interest in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. 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 hearing and waivers of participation 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). When the United States receives notification of a scheduling decision pursuant to Article 2 of the 1971 Convention that a drug or other substance has been added or transferred 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 (FDCA) meet the requirements of the

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), the 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).

schedule specified in the notification with respect to the specific drug or substance.

21 U.S.C. 811(d)(3). If such requirements are not met by such existing controls and the Secretary of HHS concurs in the scheduling decision, the Secretary shall recommend to the Attorney General that he initiate proceedings for scheduling the drug or substance under the appropriate schedule pursuant to 21 U.S.C. 811(a) and (b). 21 U.S.C.

811(d)(3)(B). Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, add to such a schedule or transfer between such schedules any drug or other substance, if he finds that such drug or other substance has a potential for abuse, and makes with respect to such drug or other substance 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 (Administrator). 28 CFR 0.100.

Background

4,4'-dimethylaminorex (4,4'-DMAR) is a synthetic stimulant drug that is structurally related to 4-methylaminorex (4-MAR), a schedule I substance in the United States and listed as a schedule I substance in the 1971 Convention. 4,4'-DMAR first emerged on the illicit drug market in December 2012 in the Netherlands. 4,4'-DMAR can be purchased through websites selling "research chemicals" and is typically sold as a powder or tablet. Based on drug user forum information presented in the scientific literature and through the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and World Health Organization (WHO) reviews, it appears that the most common routes of administration for 4,4'-DMAR are via nasal insufflation and oral ingestion. There is limited information with respect to the pharmacological properties of

4,4'-DMAR. *In vitro* studies have reported that exposure to 4,4'-DMAR results in dopamine, norepinephrine, and serotonin release at dopamine, norepinephrine, and serotonin transporters, respectively, and the dose levels are comparable to other known stimulant drugs. There are no animal or human studies that have examined dependence potential associated with 4,4'-DMAR. Due to the large number of known fatalities (46 known fatalities in several European countries since 2013) associated with 4,4'-DMAR, the United Kingdom's Advisory Council on the Misuse of Drugs (ACMD), EMCDDA, and the WHO stated that 4,4'-DMAR carries a substantial risk to the public health. Adverse symptoms such as agitation, increased body temperature, respiratory distress, and cardiac arrest have been reported in 4,4'-DMAR-related drug overdoses and deaths. In most of these deaths and overdoses, other drugs were also detected.

In November 2015, the Director-General of the WHO recommended to the Secretary-General of the United Nations that 4,4'-DMAR be placed in schedule II of the 1971 Convention, as 4,4'-DMAR produces a spectrum of pharmacological effects similar to that of psychomotor stimulants in schedule II of the 1971 Convention, and has dependence and abuse potential. On May 17, 2016, the Secretary-General of the United Nations advised the Secretary of State of the United States that during its 59th Session on March 2016, the Commission on Narcotic Drugs (CND) voted to place 4,4'-dimethylaminorex (4,4'-DMAR) in schedule II of the 1971 Convention on Psychotropic Substances (CND Dec/59/5).

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 4,4'-DMAR. This license requirement is accomplished by the CSA's registration requirement as set forth in 21 U.S.C. 822, 823, 957, 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's export and import provisions established in 21 U.S.C. 952, 953, 957, 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 Secretary-General of the United Nations, that it prohibits the importation of a substance in schedule II, III, or IV of the 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 notifying country. This requirement is also accomplished by the CSA's export provisions 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 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-psychoactive 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.

Proposed Determination to Schedule 4,4'-DMAR

Pursuant to 21 U.S.C. 811(b), DEA gathered the necessary data on 4,4'-DMAR and on March 21, 2017, submitted it to the Assistant Secretary for Health of HHS with a request for a scientific and medical evaluation of available information and a scheduling recommendation for 4,4'-DMAR. On October 12, 2018, HHS provided to DEA a scientific and medical evaluation entitled “Basis for the Recommendation to Place 4,4'-Dimethylaminorex (4,4'-DMAR) and its 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 4,4'-DMAR 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 document 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 <http://www.regulations.gov> under docket number “DEA-498.”

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 4,4'-DMAR, DEA also considered all other relevant data regarding 4,4'-DMAR's actual or relative potential for abuse. The term "abuse" is not defined in the CSA, however, the legislative history of the CSA suggests the following be considered when 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.*

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.

DEA reviewed the scientific and medical evaluation provided by HHS and all other data relevant to the abuse potential of 4,4'-DMAR. These data as presented below demonstrate that 4,4'-DMAR has a high potential for abuse.

a. Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

4,4'-DMAR is not currently approved for medical use in the United States. There are currently no data regarding 4,4'-DMAR abuse in the United States. Since 2013, 46 fatalities in which 4,4'-DMAR was detected were reported in several European countries including Hungary, Poland, and the United Kingdom (UK). As noted by HHS, all but one of these fatalities involved the concomitant use of other drugs, typically stimulants. Regardless, 4,4'-DMAR was still determined to be a contributing factor to their deaths (Factor 6).

DEA further gathered and evaluated available information from its forensic laboratory databases such as STARLiMS³, System to Retrieve Information from Drug Evidence (STRIDE)⁴, and the National Forensic Laboratory Information System (NFLIS)⁵. According to these databases, there are no known reports of 4,4'-DMAR related drug seizures in the United States.

Although 4,4'-DMAR has not been seized in the United States, there have been numerous reports of seizures of the substance in Europe. 4,4'-DMAR was first

³ STARLiMS is a laboratory information management system that systematically collects results from drug chemistry analyses conducted by DEA laboratories. On October 1, 2014, STARLiMS replaced System to Retrieve Information from Drug Evidence (STRIDE) as the DEA laboratory drug evidence data system of record.

⁴ STRIDE is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from DEA, other federal agencies, and some local law enforcement agencies.

⁵ The National Forensic Laboratory Information System (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.

encountered in a customs seizure in the Netherlands in December 2012. The EMCDDA reported in 2014 that there was one internet site that offered 4,4'-DMAR for sale. Since the initial report of the 4,4'-DMAR seizure in the Netherlands, there have been reports of seizures in other European nations including Denmark, Finland, Hungary, the Netherlands, Romania, Sweden, and the UK in 2014. Furthermore, it was reported that organized crime groups in Hungary are involved in the trafficking and distribution of 4,4'-DMAR.

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

According to HHS, 4,4'-DMAR is not an FDA-approved drug product for treatment in the United States and there appear to be no legitimate sources for 4,4'-DMAR as a marketed drug.

The NFLIS, STRIDE, and STARLiMS databases did not contain any reports of 4,4'-DMAR when queried in March 2019. This suggests that 4,4'-DMAR is not trafficked in the United States. Because 4,4'-DMAR is not approved as a drug for medical use in the United States, there appear to be no legitimate drug channels from which 4,4'-DMAR can be diverted.

According to HHS, 4,4'-DMAR can be purchased from several internet sources as a research chemical. Although it is likely that some individuals with abuse-related disorders obtained 4,4'-DMAR from these internet sources, findings have indicated that the majority of the fatalities associated with 4,4'-DMAR were the result of the user being sold what they thought was 3, 4-methylenedioxy-methamphetamine (MDMA) from their illicit source as opposed to users obtaining 4,4'-DMAR directly from these websites.

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 drugs.

4,4'-DMAR is not approved for medical use in the United States and is not formulated or available for clinical use. As noted by HHS, law enforcement seizures and anecdotal internet user experience posts (drugs-forum.com and bluelight.org) indicate that individuals are taking 4,4'-DMAR without medical advice from a licensed practitioner.

d. The substance 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 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.

As stated by HHS, 4,4'-DMAR is a derivative of substances that are in schedule I of the 1971 Convention and substances that are in schedule I of the CSA. HHS further states that the substances in schedule I of the 1971 Convention and of the CSA are known to have high potential for abuse. 4,4'-DMAR is similar in both its mechanism of action and its high potential for abuse to other scheduled compounds including 4-MAR (schedule I of the 1971 Convention and schedule I of the CSA) and aminorex (schedule I of the CSA). 4,4'-DMAR, 4-MAR, and aminorex have all been shown to increase neurotransmitter levels within the central nervous system resulting in a stimulant effect. Although there are no clinical studies on 4,4'-DMAR, extrapolated animal studies indicate its abuse and dependence potential. HHS concluded that 4,4'-DMAR has a

similar potential for abuse as substances already controlled internationally and federally in the United States.

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

There are few pharmacological studies conducted on 4,4'-DMAR and no abuse related or clinical studies in human subjects have been conducted on this substance. 4,4'-DMAR is structurally similar to aminorex and both share a similar mechanism of pharmacological action. The abuse potential of aminorex was evaluated in monkeys using drug self-administration or drug discrimination assays. The results showed that monkeys self-administered aminorex more than saline and similar to methohexital, a positive control agent. In drug discrimination assays in animals trained to distinguish *d*-amphetamine or pentobarbital from saline, aminorex fully substituted for the discriminative stimulus effects of *d*-amphetamine but produced little pentobarbital appropriate responding. Furthermore, aminorex can stimulate locomotor activity and increased the physiological dependence of rats taking pentobarbital. These data suggest that aminorex has dependence liability similar to that of amphetamine. 4-MAR with structural similarity to aminorex and 4,4'-DMAR has also been reported to be self-administered by monkeys. The structural and pharmacological similarities of 4,4'-DMAR with substances known to have high abuse potential suggest that 4,4'-DMAR itself has high abuse potential.

As described by HHS, *in vitro* studies showed that 4,4'-DMAR, similar to other controlled substances such as amphetamine, aminorex and MDMA, affects the functions of monoamine transporters. An *in vitro* study in isolated brain synaptosomes from Sprague-Dawley rats evaluated the functional activity of 4,4'-DMAR and

several other stimulant drugs including *d*-amphetamine, aminorex, (\pm)-*cis*-4-MAR, and (\pm)-*cis*-4,4'-DMAR. All tested drugs evoked release of monoamines through the three monoamine transporters, namely dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT). They are also potent at DAT and NET, indicating their potential to release dopamine and norepinephrine in the central nervous system (CNS). But, their potencies at the SERT transport are different and varied by more than 100-fold. (\pm)-*cis*-4,4'-DMAR was the most potent drug at SERT, with an EC₅₀ value of 18.5 nM, similar to its potencies at DAT (8.6 nM) and NET (26.9 nM). The data from these studies revealed that (\pm)-*cis*-4,4'-DMAR is a non-selective releaser of dopamine, norepinephrine, and serotonin and that it is more potent in releasing serotonin than amphetamine. Another *in vitro* study compared the potencies of *cis* and *trans* isomers of 4,4'-DMAR against 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) in releasing monoamines in rat brain synaptosomal preparations. It showed that *cis*-4,4'-DMAR is 2- to 3-fold more potent than *trans*-4,4'-DMAR in releasing dopamine or norepinephrine. The study also revealed that both isomers of 4,4'-DMAR are about 4- to 10-fold more potent than (+)-MDMA in releasing dopamine, norepinephrine, or serotonin.

Based on the review of both DEA and HHS, no clinical studies have been performed to evaluate the effects of 4,4'-DMAR in human subjects. Anecdotal reports of 4,4'-DMAR use reveal that insufflation and oral consumption of tablets are the major methods of administration. Reports of injection were also noted. According to the user reports from websites (e.g., bluelight.org and drug-forum.com), oral and insufflation doses range from 10 to 200 mg and from 10 to 65 mg,

respectively. Euphoria, stimulation, happiness, and increased sociability were reported to be the desired effects of 4,4'-DMAR. Drug use discussion forums report the desired effects begin within 8-60 minutes and the peak was in approximately 3 hours. 4,4'-DMAR at higher doses produced adverse effects including nausea, dysphoria, agitation, psychosis, tachycardia, hypertension, breathing problems, convulsions, and cardiac arrest. Although there are indications of 4,4'-DMAR's potential to cause serotonin syndrome, poly-drug use with substances that produce serotonergic effects confound these reports.

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

Chemistry

The molecular formula of 4,4'-DMAR is $C_{11}H_{14}N_2O$ and it has a molecular weight of 190.24 g/mol. 4,4'-DMAR is a synthetic substituted oxazoline derivative. The oxazoline structure consists of a five-membered ring containing an oxygen (O) atom at the 1-position and a nitrogen (N) atom at the 3-position. The structure of 4,4'-DMAR has two chiral centers, C4 and C5, in the oxazoline ring. Therefore, it may exist as four stereoisomers known as (4*S*,5*S*), (4*S*,5*R*), (4*R*,5*S*), and (4*R*,5*R*). 4,4'-DMAR is structurally related to *cis* 4-methylaminorex (*cis* 4-MAR) which is a psychostimulant. 4-MAR is currently a schedule I substance in the United States and is listed as a schedule I substance under the 1971 Convention.

The synthesis of 4,4'-DMAR is a complex process requiring many steps. Both (±)-*cis* 4,4'-DMAR and (±)-*trans* 4,4'-DMAR are synthesized by the cyclization of 2-amino-1-(4-methylphenyl) propan-1-ol (also known as 4'-methylnorepinephrine). The agent used for cyclization determines the synthesis of one isomer over the other. The synthetic

process of the (\pm)-*cis*-4,4'-DMAR isomers requires the use of anhydrous sodium acetate, methanol, and sodium carbonate in the final step, whereas the synthesis of the (\pm)-*trans*-4,4'-DMAR isomers requires 2-amino-1-(4-methylphenyl)propan-1-ol, potassium cyanate, water, hydrochloric acid, sodium carbonate, dichloromethane, and methanol. These substances are available for purchase through internet sources; however, the equipment and knowledge required make it difficult for an average individual to synthesize this substance.

Toxicology and Pharmacokinetics

Based on the evaluation of both DEA and HHS, there have been no non-clinical or clinical studies to directly evaluate the toxicology of 4,4'-DMAR. The toxicological data are from anecdotal reports or from fatalities in which 4,4'-DMAR was implicated as a contributory factor. Emergency Room visits and death reports revealed that 4,4'-DMAR consumption produces adverse health effects including agitation, tachycardia, hypertension, breathing problems, convulsions, and cardiac arrest. 4,4'-DMAR is believed to be a contributing factor in several deaths in Europe. Since 2013, at least 46 known fatalities have been associated with the use of 4,4'-DMAR in several European nations including Hungary, Poland, and the UK. The reported mean blood concentration of 4,4'-DMAR in 27 fatalities was 2.04 mg/L, while the range of urine concentrations in three of the fatalities ranged from 5.93 to 43.49 mg/L.

As mentioned by HHS, there are no human pharmacokinetic data for 4,4'-DMAR. A preliminary study in rats showed that *cis*-4,4'-DMAR administered intravenously (1 mg/kg) rapidly enters the brain after 5 minutes.

4. Its History and Current Pattern of Abuse:

HHS and DEA's review indicates that several European countries have reported drug seizures in which 4,4'-DMAR was detected in either powder or tablet form. As mentioned in the HHS review, customs authorities first detected 4,4'-DMAR in the Netherlands in 2012, in a seized drug powder that came from India. In 2013, Hungarian authorities reported at least 78 seizures of 4,4'-DMAR alone or mixed with other stimulants (mainly cathinones), both in powder and tablet form, which originated from China. Romania, Sweden, Denmark, and Finland also reported multiple drug seizures containing various amounts of 4,4'-DMAR since 2013. According to HHS, two published studies in 2015 examined the availability of 4,4'-DMAR using internet search engines and reported that there was one internet site that sold 4,4'-DMAR, which is currently still available.

There have been no published studies addressing the prevalence and pattern of abuse of 4,4'-DMAR. 4,4'-DMAR is a fine white powder that can be pressed into tablets. The most common routes of administration for 4,4'-DMAR are oral ingestion and nasal insufflation. According to user reports, doses of 4,4'-DMAR range from 10 to 200 mg and 10 to 65 mg for oral administration and insufflation, respectively.

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

There are no studies directly monitoring the scope and duration of use or abuse of 4,4'-DMAR. However, some internet websites contain anecdotal reports indicating that users can purchase 4,4'-DMAR from online sources as a research chemical. Fatalities reports reveal that most users believed they used another drug, such as MDMA, which is typically obtained illicitly from drug dealers. A published paper in 2015 reported at least one online retailer selling 4,4'-DMAR at a minimum amount of

500 mg for €36.08/g. The EMCDDA report also identified two internet sources for 4,4'-DMAR.

HHS stated that no specific epidemiological reports regarding the significance of abuse of 4,4'-DMAR are available. The reported cases of 4,4'-DMAR-associated deaths suggest that many of these drug users assumed that they were using MDMA. Thus, the majority of instances of abuse appear to be unintentional (see Factor 6).

Additionally, based on DEA's review, there is no evidence of 4,4'-DMAR abuse in the United States. DEA's STRIDE/STARLiMS and the NFLIS databases as queried in March 2019 had no reports of 4,4'-DMAR, suggesting that it is not trafficked in the United States. The first seizure of 4,4'-DMAR (500 grams of white powder) occurred in the Netherlands in 2012; subsequently a small seizure was made in Finland in 2013. Hungary reported 41 seizures totaling 1,852 tablets and 37 seizures totaling 377 grams of powder between June and October of 2013. In twenty percent of these seizures (both powder and tablets), 4,4'-DMAR was mixed with other illicit substances such as synthetic cathinones and synthetic cannabinoids. In the subsequent years, 4,4'-DMAR was reported in Denmark, Finland, France, Hungary, the Netherlands, Poland, Romania, Sweden, and the UK. These seizures in Europe have been small in size. Because synthetic cathinones and synthetic cannabinoids are being widely abused in the United States, it is possible that the abuse of 4,4'-DMAR mixed with these substances may occur domestically if 4,4'-DMAR were to be trafficked and abused in the United States.

6. *What, if any, Risk There is to the Public Health:*

Based on the review of both HHS and DEA, use of 4,4'-DMAR has been associated with at least 31 serious adverse events and 46 fatalities throughout Europe since

2013. These serious adverse events and fatalities are the result of unintentional consumption of 4,4'-DMAR. These individuals bought what they thought to be another substance such as MDMA, cocaine, or mephedrone from websites. According to HHS, the so called “psychonauts” who purchase substances for exploratory purposes appear to be buying 4,4'-DMAR from research chemical websites.

According to the medical examiner reports mentioned in 2014 EMCDDA Risk Assessment, of the 23 fatalities, one was the result of 4,4'-DMAR alone; in two fatalities, 4,4'-DMAR had a major role, and in the remaining 20 cases, 4,4'-DMAR mixed with other drugs likely contributed to deaths. Prior to their deaths, many of these individuals showed symptoms similar to sympathomimetic toxicity, which included agitation, aggression, seizures, and hyperthermia. Another study further analyzed the EMCDDA and ACMD’s epidemiological data and revealed that in 31 fatalities associated with 4,4'-DMAR, 22 were male, 8 were female, and 1 was unknown. Many of these individuals also had ingested multiple drugs. Combining 4,4'-DMAR with other drugs may contribute to fatal overdoses and pose a risk to the public health.

7. Its Psychic or Physiological Dependence Liability:

There are no non-clinical or clinical studies examining the psychic or physiological dependence liability of 4,4'-DMAR. Drug abuse-associated internet forums or drug treatment facilities had no mentions of dependence liability associated with 4,4'-DMAR. Although direct evidence regarding the psychic and physiologic dependence liability of 4,4'-DMAR is lacking, information on substances that have a pharmacological mechanism of action similar to that of 4,4'-DMAR can be

used to infer the dependence potential of this substance. As stated in Factor 2, 4,4'-DMAR shares a mechanism of action with aminorex, a structurally related substance. Aminorex increases locomotor activity and the physiological dependence of rats taking pentobarbital. Aminorex has dependence liability similar to the stimulant amphetamine. Because of similarities in structure and pharmacology between aminorex and 4,4'-DMAR, it can be inferred that 4,4'-DMAR will have high psychic and physiological dependence liability similar to that of *d*-amphetamine.

8. *Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA:*

DEA and HHS find that 4,4'-DMAR is not an immediate precursor of a substance already controlled under the CSA.

Conclusion:

Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and based 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 4,4'-DMAR. As such, DEA hereby proposes to schedule 4,4'-DMAR as a schedule I controlled substance under the CSA.

Proposed Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as schedule 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 Assistant Secretary for Health of HHS and review of

all available data, the Acting Administrator of DEA (Acting Administrator), pursuant to 21 U.S.C. 812(b)(1), finds that:

(1) 4,4'-DMAR has a high potential for abuse. There are no non-clinical or clinical studies directly evaluating the abuse potential of 4,4'-DMAR. However, 4,4'-DMAR is chemically similar to aminorex (schedule I) and *in vitro* activity assays using brain synaptosomes indicate that 4,4'-DMAR has similar pharmacological activity to *d*-amphetamine (schedule II), aminorex (schedule I), and MDMA (schedule I). More specifically, 4,4'-DMAR acts as a more potent releaser of dopamine, norepinephrine, and serotonin than substances that are listed in schedules I and II of the CSA. 4,4'-DMAR has been detected in several drug seizures in several European countries. These reports correlate with 46 deaths in which 4,4'-DMAR played a contributory role. The data provides supportive evidence that 4,4'-DMAR has a high potential for abuse that is similar to substances in schedule I or II of the CSA

(2) 4,4'-DMAR has no currently accepted medical use in treatment in the United States. There are no approved New Drug Applications for 4,4'-DMAR and no known therapeutic applications for 4,4'-DMAR in the United States. Therefore, 4,4'-DMAR has no currently accepted medical use in treatment in the United States.⁶

⁶ Although there is no evidence suggesting that 4,4'-DMAR 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.

(3) There is a lack of accepted safety for use of 4,4'-DMAR under medical supervision. Because 4,4'-DMAR 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 4,4'-DMAR under medical supervision.

Based on these findings, the Acting Administrator concludes that 4,4'-DMAR warrants control in schedule I of the CSA. 21 U.S.C. 812(b)(1). More precisely, because of its stimulant effects, and because it may produce stimulant-like tolerance and dependence in humans, DEA is proposing to place 4,4'-DMAR in 21 CFR 1308.11(f) (the stimulants category of schedule I). As such, the proposed control of 4,4'-DMAR includes the substance as well as its salts, isomers, and salts of isomers.

Requirements for Handling 4,4'-DMAR

If this rule is finalized as proposed, 4,4'-DMAR 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 of 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) 4,4'-DMAR, or who desires to handle 4,4'-DMAR, would need to be registered with DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, 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 4,4'-

DMAR, and is not registered with DEA, would need to submit an application for registration and may not continue to handle 4,4'-DMAR after 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 all quantities of currently held 4,4'-DMAR, or transfer all quantities of currently held 4,4'-DMAR 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, 4,4'-DMAR 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.* 4,4'-DMAR would be subject to schedule I security requirements and would need to be handled and stored in accordance with 21 CFR 1301.71–1301.93 as of the effective date of a final scheduling action.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of 4,4'-DMAR would need to be in compliance with 21 U.S.C. 825 and 958(e), 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 4,4'-DMAR 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 4,4'-DMAR on the effective date of a final scheduling action would be required to take an inventory of

4,4'-DMAR on hand at that time, pursuant to 21 U.S.C. 827 and 958, 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 4,4'-DMAR) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827 and 958, 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 an inventory of all controlled substances (including 4,4'-DMAR) on hand every two years, pursuant to 21 U.S.C. 827 and 958, 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 pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR parts 1304, 1312, and 1317, as of the effective date of a final scheduling action. Manufacturers and distributors would be required to submit reports regarding 4,4'-DMAR to the Automation of Reports and Consolidated Order System (ARCOS) 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 4,4'-DMAR would be required to comply with order form requirements, pursuant to 21 U.S.C. 828, and in accordance with 21 CFR part 1305, as of the effective date of a final scheduling action.

9. *Importation and Exportation.* All importation and exportation of 4,4'-DMAR 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 4,4'-DMAR 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.

Regulatory Analyses

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

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 (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

This rulemaking is not an Executive Order 13771 regulatory action because this rule is not significant under Executive Order 12866.

Executive Order 12988, Civil Justice Reform

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988, Civil Justice Reform, 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 Executive Order 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or 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 Executive Order 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.

Regulatory Flexibility Act

The Acting Administrator, in accordance with the Regulatory Flexibility Act (RFA), 5 U.S.C. 601–602, 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 4,4'-DMAR (Chemical name: 4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine), including its salts, isomers, and salts of isomers, whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule I of the CSA. 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 4,4'-DMAR.

According to HHS, 4,4'-DMAR has a 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 4,4'-DMAR in the United States. Additionally, queries of DEA's STRIDE/STARLiMS and the NFLIS databases in February, 2020, did not generate any reports of 4,4'-DMAR, suggesting that it is not trafficked in the United States. Therefore, DEA estimates that no U.S. entity currently handles 4,4'-DMAR and does not expect any U.S. entity to handle 4,4'-DMAR in the foreseeable future. DEA concludes that no U.S. entity would be affected by this rule if finalized. As such, the proposed rule will not have a significant effect on a substantial number of small entities.

Duplicative, overlapping, and conflicting rules

DEA is the only agency with authority to schedule drugs under the CSA. DEA has not identified any duplicative, overlapping, or conflicting rules with the proposed rule.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 *et seq.*, DEA has determined and certifies that this 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 for inflation) in any 1 year * * *.” Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act

This action does not impose a new collection of information requirement under the Paperwork Reduction Act, 44 U.S.C. 3501–3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). This rule will not result in: an annual effect on the economy of \$100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based companies to compete with foreign-based companies in domestic and export markets.

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 to read 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), unless otherwise noted.

2. In § 1308.11, redesignate paragraphs (f)(4) through (f)(8) as paragraphs (f)(5) through (f)(9) and add a new paragraph (f)(4) to read as follows:

§ 1308.11 Schedule I.

* * * * *

(f) * * *

(4) 4,4'-Dimethylaminorex (4,4'-DMAR; 4,5-dihydro-4-methyl-5-(4-methylphenyl)-2-oxazolamine; 4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine)..... 1595

* * * * *

Uttam Dhillon,
Acting Administrator
[FR Doc. 2020-07095 Filed: 4/6/2020 8:45 am; Publication Date: 4/7/2020]