U.S. Department of Justice

Drug Enforcement Administration

Schedules of Controlled Substance: Placement of 4,4'-Dimethylaminorex (4,4'-DMAR) into Schedule I

Background, Data, and Analysis:

Eight Factors Determinative of Control

and Findings Pursuant to 21 U.S.C. § 812(b)

Prepared by

Diversion Control Division, Drug and Chemical Evaluation Section
Washington, D.C. 20537

February 2020

INTRODUCTION

According to the scientific and medical evaluation prepared by the Department of Health and Human Services (HHS), 4,4'-dimethylaminorex (4,4'-DMAR) is a synthetic stimulant drug and is similar in chemical structure and pharmacological properties to aminorex and 4-methylaminorex (4-MAR), schedule I substances under the Controlled Substances Act (CSA). It is also pharmacologically similar to other controlled stimulants such as amphetamine and 3,4-methylenedioxymethamphetamine (MDMA) (HHS, 2018). According to the Critical Review prepared by the World Health Organization (WHO), 4,4'-DMAR first emerged on the illicit drug market in December 2012 in the Netherlands and subsequently in several other European countries (WHO, 2015).

4,4'-DMAR is commonly abused via nasal or oral routes. Serious adverse effects including agitation, increased body temperature, respiratory distress, and cardiac arrest have been reported following the ingestion of 4,4'-DMAR (EMCDDA, 2014; 2015; WHO, 2015; HHS, 2018). At least 46 known fatalities have been associated with the use of 4,4'-DMAR worldwide. However, as noted by the Department of Health and Human Services (HHS), in all but one of these deaths, other drugs were also detected. The United Kingdom's (UK) Advisory Council on the Misuse of Drugs (ACMD), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and the World Health Organization (WHO) stated that 4,4'-DMAR carries a substantial risk to the public health.

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 (DA), norepinephrine (NE) and serotonin (5-HT) neurotransmitter release through dopamine transporters (DAT), norepinephrine transporters (NET) and serotonin transporters (SERT) that is similar to the release following administration of the known stimulant drugs such as aminorex, 4-MAR, amphetamine and MDMA (see Factor 2). Potency of 4,4'-DMAR in causing monoamine release through DAT and NET is similar to that of amphetamine and MDMA, however it is more potent in causing serotonin release through SERT (HHS, 2018).

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 on Psychotropic Substances; 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). As a signatory to this international treaty, the United States is required, by scheduling under the Controlled Substances Act (CSA), to place appropriate controls on 4,4'-DMAR to meet the requirements of the treaty.

On March 21, 2017, the Drug Enforcement Administration (DEA) requested that the Department of Health and Human Services (HHS) conduct a scientific and medical evaluation and provide a scheduling recommendation for 4,4'-DMAR pursuant to the Controlled Substances Act (CSA). 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 (HHS, 2018). 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).

The CSA requires DEA to determine whether the HHS's scientific and medical evaluation and scheduling recommendation along with other relevant data constitute substantial evidence that the substance should be scheduled pursuant to 21 U.S.C. § 811(b). Pursuant to 21 U.S.C. § 811(c), DEA reviewed the facts and all other relevant data. This document contains a summary of the relevant data, law enforcement information and a determination to place 4,4'-DMAR into schedule I of the CSA.

The information contained in this document is organized according to the eight factors as specified in 21 U.S.C. § 811(c).

Factor 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 (HHS, 2018), 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 in determining whether a particular drug or substance has a potential for abuse:[1]

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*

[1] 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.

to the health of the user or to the safety of the community.

HHS has evaluated scientific, medical, abuse and other data on 4,4'-DMAR from various sources such as scientific and medical journals and the Critical Review document on 4,4'-DMAR prepared by the WHO for evaluation by the 37th meeting of the WHO Expert Committee on Drug Dependence held in 2015 (WHO, 2015). DEA has considered HHS scientific and medical evaluation and all other relevant data including law enforcement data. The findings as they relate to 4,4'-DMAR include the following:

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. Thus any use of this substance is assumed to be illicit in nature. There are currently no data regarding 4,4'-DMAR abuse in the United States. As noted by HHS, fatalities in which 4,4'-DMAR was detected were reported in several countries in Europe (Cosbey et al, 2014; Europol, 2014; ECDD, 2015; WHO, 2015). 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) (Europol, 2014; HHS, 2018).

DEA further gathered and evaluated available information from its forensic laboratory databases such as STARLiMS[2], System to Retrieve Information from Drug Evidence (STRIDE)[3], and the National Forensic Laboratory Information System

[2] 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 DEA laboratory drug evidence data system of record.

[3] 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.

(NFLIS)[4]. 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 drug seizures in Europe. 4,4-DMAR was first encountered in a customs seizure in the Netherlands in December 2012 (WHO, 2015; EMCDDA, 2014; ACMD, 2014). As reported by the EMCDDA (2014), there was one internet site that offered 4,4'-DMAR for sale. Since the initial report of the 4,4'-DMAR drug seizure in the Netherlands, there have been reports of drug seizures in Denmark, Finland, Hungary, Poland, Romania, Sweden, France, and the United Kingdom (ACMD, 2014). Furthermore, it was reported that organized crime groups in Hungary are involved in the trafficking and distribution of 4,4'-DMAR (ACMD, 2014).

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 appears to be no legitimate sources for 4,4'-DMAR as a marketed drug. Based upon this information this characteristic of abuse potential is not applicable (HHS, 2018).

The NFLIS, STRIDE and STARLiMS databases did not contain any reports of 4,4'-DMAR when queried on February, 2020. This suggests that 4,4'-DMAR is not trafficked in the United States. 4,4'-DMAR is not approved as a drug for medical use in the United States. There appears to be no legitimate drug channels from which 4,4'-DMAR can be diverted. Thus, this indicator of abuse potential would not be applicable.

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

[4] 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.

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 MDMA from their illicit source as opposed to users obtaining 4,4'-DMAR directly from these websites. It is also unknown whether the internet sources are legitimate (EMCDDA, 2014; WHO, 2015; HHS, 2018).

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 (HHS, 2018).

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 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.

As stated by HHS, 4,4'-DMAR is a derivative of substances that are in Schedule I of the 1971 psychotropic convention and substances that are in schedule I of the CSA. HHS further states that the substances in Schedule I of the 1971 psychotropic 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 as compared to other scheduled compounds including 4-MAR (Schedule I of the 1971 United Nations Convention on Psychotropic Substances 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 (Brandt et al., 2014; Coppola and Mandala, 2015; Rothman and Baumann, 2003). According to the WHO Critical Review, although there are no clinical studies on 4,4'-DMAR, extrapolated animal studies indicate its abuse and dependence potential (WHO, 2015). HHS concluded that 4,4'-DMAR has a similar potential for abuse as substances already controlled internationally and federally in the United States (HHS, 2018).

Factor 2: Scientific Evidence of 4,4'-DMAR's Pharmacological Effects

As noted by HHS, few pharmacological studies have been conducted on 4,4'-DMAR and no abuse potential related studies in human subjects had 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 assay 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 (Woolverton et al., 1994). Authors concluded 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 (Mansbach et al., 1990). 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 (HHS, 2018).

***In Vitro* Study Findings**

As described by HHS (2018), *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, *(±)-cis*-4-MAR and (±)-*cis*-4,4'-DMAR. As shown in Table 1, all test drugs evoked release of monoamines through the three monoamine transporters namely, DAT, NET and SERT. All test drugs are 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 are different and varied by more than 100-fold. (±)-*cis*-4,4'-DMAR was the most potent drug at SERT, with an EC_{50} 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 (±)-*cis*-4,4'-DMAR is a non-selective releaser of dopamine, norepinephrine and serotonin and that it is more potent in releasing serotonin than that of amphetamine (Brandt et al., 2014; Coppola and Mondola, 2015; HHS, 2018).

Table 1. Monoamine release effects of *d*-amphetamine, aminorex, *(±)-cis*-4-MAR, and *(±)–cis*-4,4'-DMAR[5] at brain synaptosomes in *in vitro.*

Drug	DAT EC_{50} (nM)*	NET EC_{50} (nM)*	SERT EC_{50} (nM)*
d-Amphetamine	5.5 ± 0.5	8.2 ± 1.6	2602 ± 494
Aminorex	9.1 ± 0.9	15.1 ± 3.5	414 ± 78
(±)-*cis*-4-MAR	1.7 ± 0.2	4.8 ± 0.9	53.2 ± 6.8
(±)-*cis*-4,4'-DMAR	8.6 ± 1.1	26.9 ± 5.9	18.5 ± 2.8

* Data are expressed as mean± SD; N = 3-4 in triplicate (Brandt et al., 2014)

Another *in vitro* study similar to the in vitro study mentioned above compared the potencies of *cis* and *trans* isomers of 4,4'-DMAR against 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) in releasing monoamines in rat brain synaptosomal preparations. As shown in Table 2, *cis*-4,4'-DMAR is 2- to 3-fold

[5] The chemical structure of 4,4'-DMAR has two chiral centers, C4 and C5 in the oxazoline ring. Therefore, there are four stereoisomers known as (4*S*, 5*S*), (4*S*, 5*R*), (4*R*,5S), (4*R*,5*R*). The (S) and (*R*) prefix refers to the absolute configuration at the respective chiral carbons. Stereoisomers can also be expressed as (+) or (-) or by the prefix *dextro* or *levo*. The four stereoisomers of 4,4'-DMAR can be grouped into two pairs of enantiomers. One pair of enantiomers, which is known as the *(±)-cis*-4,4'-DMAR pair comprises of (4*R*,5*S*) and the (4*S*,5*R*) enantiomers. The second pair known as the *(±)-trans*-4,4'-DMAR pair consists of (4S, 5S) and (4*R*,5*R*) enantiomers. Enantiomers may differ in their interaction with receptor sites and may have a distinct pharmacological profile (Brandt et al., 2014; HHS, 2018).

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 as (+)-MDMA in causing DA, NE or 5-HT release (McLaughlin et al., 2015; HHS, 2018).

Table 2. Monoamine release effects of d-amphetamine, aminorex, *(±)-cis*-4-MAR, and *(±)–cis*-4,4'-DMAR at brain synaptosomes in *in vitro.*

Drug	DAT EC_{50} (nM)*	NET EC_{50} (nM)*	SERT EC_{50} (nM)*
(+)-MDMA	143 ± 16	98.3 ± 15.0	85.0 ± 13.3
cis-4,4'-DMAR	10.9 ± 0.7	11.8 ± 2.0	17.7 ± 2.3
trans-4,4'-DMAR	24.4 ± 2.7	31.6 ± 4.6	59.9 ± 17.2

*Data are expressed as mean ± SD; N = 3-4 in triplicate (McLaughlin et al., 2015).

Clinical Studies

As noted by HHS, no clinical studies have been conducted to evaluate the effects of 4,4'-DMAR.

Anecdotal reports of 4,4'-DMAR use reveal that insufflation and oral consumption of tablets are the major methods of its 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 (EMCDDA, 2014; 2015; HHS, 2018). Euphoria, stimulation, happiness, and increased sociability were to be the desired effects of 4,4'-DMAR. Drug users discussion forums report the onset of the desired effects to be 8-60 minutes and the peak was in approximately 3 hours (bluelight.org, drug- forum.com). 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 (e.g., ecstasy and synthetic cathinones) confound these reports (WHO, 2015; HHS, 2018).

Factor 3: The State of Current Scientific Knowledge Regarding 4,4'-DMAR

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. The Systemic International Union of Pure and Applied Chemistry (IUPAC) name for 4,4'-DMAR is 4-methyl-5-(4-methylphenyl)-4,5-dihydro-l,3-oxazol-2-amine (4,4'-dimethylaminorex). The Chemical Abstract Service (CAS) registry number of 4,4'-DMAR is 445569-01-6. 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*,5S), (4*S*,5*R*), (4*R*,5*S*), (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 United Nations Convention on Psychotropic Substances.

As mentioned in the HHS review, synthesis of 4,4'-DMAR is a complex process requiring many steps (Brandt et al., 2014; McLaughin et al., 2015; HHS, 2018). 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 (±)-*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 (±)-*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. As a research chemical, 4,4'-DMAR can be bought directly from the internet (HHS, 2018).

Toxicology and Pharmacokinetic Findings

As noted by HHS, there are no animal or human studies directly evaluating 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 (ER) visits and death reports revealed that 4,4'-DMAR consumption produces adverse health effects including agitation, tachycardia, hypertension, breathing problems, convulsions, and cardiac arrest (WHO, 2015; HHS, 2018). 4,4'-DMAR is thought to be a contributing factor in several deaths in Europe. At least 46 known fatalities have been associated with the use of 4,4'-DMAR worldwide. However, as noted by the HHS, in all but one of these deaths, other drugs were also detected. One fatality case in the United Kingdom involved only 4,4'-DMAR. In 31 fatality cases, there was evidence of poly-drug use including cannabinoids (THC), stimulants (cocaine and amphetamine), benzodiazepines, opioids and synthetic cathinones. The mean blood concentration of 4,4'-DMAR in 27 of these fatalities was 2.04 mg/L, while the range of urine concentrations in 3 of the fatalities ranged from 5.93 to 43.49 mg/L (WHO, 2015; HHS, 2018).

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 with a Cmax of 0.355 µg/mL, and a terminal half-life of 5.1 hours (Lucchetti et al., 2016). This study also investigated pharmacokinetics of *cis*-4,4'-DMAR following intraperitoneal (IP) administration of 1, 3, and 10 mg/kg doses and reported high first pass metabolizing effects and a linear increase in the plasma levels with dose. These results indicate that the metabolism of *cis*-4,4'-DMAR was not saturated at these doses (Lucchetti et al., 2016; HHS, 2018).

Factor 4: 4,4'-DMAR's History and Current Pattern of Abuse

According to the WHO Critical Review, in 2014, seizures of 4,4'-DMAR in powder or tablet form have been reported in several European countries including Denmark, Finland, Hungary, the Netherlands, Romania, Sweden and UK. 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, the 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. Two published studies examined the availability of 4,4'-DMAR using internet search engines and reported that there was one internet site that sold 4,4'-DMAR (Glanville et al, 2015; Nizar et al, 2015),which is still available. These data indicate that the abuse of 4,4'-DMAR in those European countries, at least until 2014, was limited to the European community (EMCDDA, 2014; WHO, 2015; HHS, 2018).

As noted by HHS, 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 (EMCDDA, 2014; 2015; Glanville et al., 2015; HHS, 2018).

Factor 5: The Scope, Duration, and Significance of Abuse of 4,4'-DMAR

As stated by HHS, 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 are typically obtained illicitly from drug dealers (HHS, 2018).

According to a published paper in 2015, Nizar et al (2015) conducted internet search using the terms "buy 4-methylaminorex" and "buy 4,4'-dimethylaminorex" and found at least one online retailer selling 4,4'-DMAR a minimum amount of 500 mg for €36.08/g (Nizar et al., 2015). EMCDDA identified two internet sources for 4,4'-DMAR (EMCDDA, 2014). According to the above two reports, in 2014, 4,4'-DMAR was available only from limited internet sources.

According to HHS, no specific epidemiological reports regarding the significance of abuse of 4,4'-DMAR are available. The reported cases of 4,4'-DMAR-assocaited deaths suggests that many of these drug users assumed that they were using ecstasy (MDMA). Thus, majority of instances of abuse appear to be unintentional (see Factor 6) (WHO, 2015; HHS, 2018).

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 on November 2018 had no reports of 4,4'-DMAR, suggesting that it is not trafficked in the United States. As noted by HHS, according to the 2014 EMCDDA report, the first seizure of 4,4'-DMAR (500 grams of white powder) occurred in the Netherlands in 2012, subsequently a small seizure in Finland in 2013. Hungary reported 41 seizures of 1,852 tablets and 37 seizures of 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, Netherlands, Poland, Romania, Sweden and the U.K. These seizures in Europe have been small in size (EMCDDA, 2014; HHS, 2018). 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 the 4,4'-DMAR were to be trafficked and abused in the United States

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

As stated in the HHS review, use of 4,4'-DMAR has led to several intoxications and fatalities throughout Europe (HHS, 2018). These intoxications 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. The so called "psychonauts" who purchase substances for exploratory purposes, appear to be buying 4,4'-DMAR from research chemical websites.

As stated by HHS, 4,4'-DMAR may have played a role in 46 fatalities; Hungary (8), Poland (1), and UK (37) (ACMD, 2014; EMCDDA, 2014; WHO, 2015). According to medical examiner reports, of the 23 fatalities, one was the result of 4,4'-DMAR alone; in 2 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 (EMCDDA, 2014; 2015; HHS 2018). Prior to their death, many of these decedents showed symptoms similar to sympathomimetic toxicity, which included agitation, aggression, seizures, and hyperthermia (HHS, 2018). According to the epidemiological data available for 31 fatalities associated with 4,4'-DMAR, 22 were male, 8 were female, and 1 is unknown. Toxicological analyses of femoral blood obtained at autopsy from 27 decedents found the mean blood concentration of 4,4'-DMAR as 2.04 mg/L (HHS, 2018). Many of these individuals also had other drugs such as cocaine, amphetamines, cannabis, benzodiazepines, anti-depressants, anti-psychotics, opioids and synthetic cathinones (HHS, 2018). Although it is difficult to determine the dangers associated with the use of 4,4'-DMAR alone, 4,4'-DMAR in combination with other drugs can contribute to fatal overdoses and pose a risk to the public health (Coppola and Mondola, 2015; HHS, 2018).

Factor 7: The Drug's Psychic or Physiological Dependence Liability

As stated in the HHS review, there are no non-clinical or clinical studies examining the psychic or psychological dependence liability of 4,4'-DMAR (HHS, , 2018). 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 physiological dependence liability of 4,4'-DMAR is lacking, information on substances that have pharmacological mechanism of action similar to that of 4,4'-DMAR can be used to infer dependence potential of this substance.

As stated in Factor 2 in the HHS review, 4,4'-DMAR shares a mechanism of action with aminorex, a structurally related substance. Aminorex increases locomotor activity, and it increases the physiological dependence of rats taking pentobarbital (Woolverton et al., 1994, HHS, 2018). 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 (Clemow and Walker, 2014, HHS, 2018).

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

4,4'-DMAR is not an immediate precursor of any controlled substance of the CSA as defined by 21 U.S.C. § 802(23).

FINDINGS

21 U.S.C. § 812(b) requires the evaluation of a substance's abuse potential, accepted medical use, and safety for use under medical supervision for placement in the CSA as a controlled substance. After consideration of the above eight factors

determinative of control of a substance (21 U.S.C. § 811(c)), and a review of the scientific and medical evaluation and scheduling recommendation provided by HHS (HHS, 2018) in concurrence with the National Institute on Drug Abuse (NIDA), DEA finds that 4,4'-DMAR meets the following criteria for placement in schedule I of the CSA under 21 U.S.C. § 812(b)(1).

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). Non-clinical pharmacological assays (*in vitro* activity assays) using brain synaptosomes indicated that 4,4'-DMAR has pharmacological effects similar to that of *d*-amphetamine (schedule II), aminorex (schedule I) and MDMA (schedule I). Furthermore, 4,4'-DMAR is more potent than substances that are listed in schedule I and II of the CSA in releasing of dopamine, norepinephrine and serotonin.

4,4'-DMAR has been encountered by the law enforcement in several European countries. This substance may have played a contributory role in 46 deaths in several European countries. These data support that 4,4'-DMAR may have a high potential for abuse that is similar to that of 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 FDA-approved drug products containing 4,4'-DMAR for any clinical indication. According to HHS, there are no clinical studies or petitioners that claim an accepted medical use in the United States. Therefore, 4,4'-DMAR has no currently accepted medical use in treatment in the United States.

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

4,4’-DMAR has no accepted medical use in the United States and it has not been investigated as a new drug. Therefore there is a lack of accepted safety for use of 4,4’-DMAR under medical supervision.

REFERENCES

1. Advisory Council on the Misuse of Drugs (ACMD) (2014), Report on the synthetic stimulant known as 4,4'-DMAR, Unite Kingdom.

2. Brandt SD, Baumann MH, Partilla JS, Kavanagh PV, Power JD, Talbot B, Twamley B, Mahony O, O’Brien J, Elliott SP, Archer RP, Patrick J, Singh K, Dempster NM, Cosbey SH (2014), Characterization of a novel and potentially lethal designer drug (±)-cis-para-methyl-4-methylaminorex (4,4’-DMAR, or ‘Serotoni’). Drug Test Anal 6: 684-695.

3. Clemow DB, Walker DJ (2014), The potential for misuse and abuse of medications in ADHD: a review. Postgrad Med 126:64-81.

4. Coppola M, Mondola R (2015), 4,4'-DMAR: chemistry, pharmacology and toxicology of a new synthetic stimulant of abuse. Basic Clin Pharmacol Toxicol. 2015; 117:26-30.

5. Cosbey S, Kirk S, McNaul M, Peters L, Prentice B, Quinn A, Elliott SP, Brandt SD and Archer RP (2014), Multiple Fatalities Involving a New Designer Drug: Para-Methyl-4- Methylaminorex. J Anal Toxicol 38:383-384.

6. Department of Health and Human Services (2018), “Basis for the Recommendation to Place 4,4’-Dimethylaminorex (4,4’-DMAR) and its salts in Schedule I of the Controlled Substances Act”, October 12, 2018

7. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2014), Risk Assessment Report of a new psychoactive substance: 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4’-dimethylaminorex, 4,4’-DMAR).

8. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2015), 4,4’-DMAR. Report on the risk assessment of 4,4’-DMAR in the framework of the Council Decision on new psychoactive substances.

9. Glanville J, Dargan PI and Wood DM (2015), 4-methyl-5-(4-methylphenyl)-45-dihydrooxazol-2-amine (4,4'-DMAR, 4,4'-dimethylaminorex): availability,

prevalence of use, desired effects and acute toxicity. Hum Psychopharmacol 30:193-198.

10. Lucchetti J, Marzo CM, Di Clemente A, Cervo Land Gobbi M (2017), A validated, sensitive HPLC-MS/MS method for quantification of cis-para-methyl-4-methylaminorex (cis-4,4'- DMAR) in rat and human plasma: application to pharmacokinetic studies in rats. Drug Test Anal. 9:870-879

11. Mansbach RS, Sannerud CA, Griffiths RR, Balster RL, Harris LS (1990), Intravenous Self- Administration of 4-Methylaminorex in Primates. Drug Alcohol Depen 26:137-144.

12. McLaughlin G, Morris N, Kavanagh PV, Power JD, Twamley B, O'Brien J, Talbot B, Dowling G, Mahony O, Brandt SD, Patrick J, Archer RP, Parrilla JS, Baumann MH (2015). Synthesis, characterization, and monoamine transporter activity of the new psychoactive substance 3',4'-methylenedioxy-4-methylaminorex (MDMAR). Drug Test Anal, 7:555-564.

13. Nizar H, Dargan PI and Wood DM (2015), Using internet snapshot surveys to enhance our understanding of the availability of the novel psychoactive substance 4-methylaminorex and 4,4'-dimethylaminorex. J Med Toxicol 11:80-84.

14. Rothman RB and Baumann MH (2003), Monoamine transporters and psychostimulant drugs. Eur J Pharmacol 479:23-40.

15. Woolverton WL, Massey BW, Winger G, Patrick GA, Harris LS (1994), Evaluation of the abuse liability of aminorex. Drug Alcohol Depend 36:187-192.

16. World Health Organization (WHO) (2015), Para-methyl-4-methylaminorex (4,4'-DMAR). Critical Review Report. Agenda Item 5.5. Expert Committee on Drug Dependence, 37th Meeting, Geneva, November 16-20, 2015