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Lynne Featherstone MP, Minister for Crime Prevention
Home Office
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14 November 2014

Dear Minister,

RE: ACMD's recommendation on the synthetic stimulant 4,4'-DMAR

I am pleased to enclose the Advisory Council on the Misuse of Drugs' report on the synthetic stimulant known as "4,4'-DMAR". This novel psychoactive substance was first detected in Europe in December 2012 and has since caused deaths in Europe, including the UK and most notably in Northern Ireland.


The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol have published a joint report on the potency and toxicity of 4,4'-DMAR. The EMCDDA has also recently published its risk assessment of 4,4'-DMAR¹.

Although the ACMD has not found an indication of its current availability in the UK, the Advisory Council recommends the permanent control of this stimulant based on the fatalities it has already caused in the UK and in Europe. 4,4'-DMAR is an analogue of 4-methyl-aminorex, which is already controlled as a Class A, Schedule 1 compound.

The ACMD recommends that 4,4'-DMAR be controlled under the Misuse of Drugs Act 1971 as a **Class A** substance and scheduled under **Schedule 1** of the Misuse of Drugs Regulations 2001 (as amended).

¹ <http://www.emcdda.europa.eu/publications/joint-reports/4-4-DMAR>

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Les Iversen'. The signature is written in a cursive style with a large initial 'L'.

Professor Les Iversen
ACMD Chair

CC: Rt Hon Theresa May MP, Home Secretary

ACMD Report on the Synthetic Stimulant 4,4'-DMAR

1. Introduction

1.1. 4,4'-DMAR is a synthetic substituted oxazoline compound [EMCDDA-Europol report 2014] (see figure 1). It is an analogue of aminorex (figure 2) and 4-methylaminorex (4-MAR) (figure 3). Aminorex and 4-MAR are controlled in the UK as Class C, Schedule 1 and Class A, Schedule 1 respectively.

1.2. 4,4'-DMAR was first detected in Europe in the Netherlands in December 2012, in the UK it has been detected in seizures in Northern Ireland and Scotland [EMCDDA Europol 2014]. *In vitro* studies have shown that 4,4'-DMAR is a stimulant drug. There are reports of deaths associated with 4,4'-DMAR from the UK and a number of other European countries.

2. Chemical description

2.1. The IUPAC name for 4,4'-DMAR is 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine.

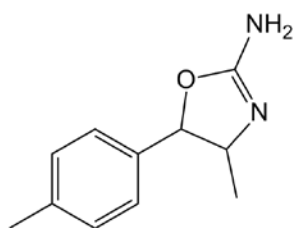


Figure 1: Chemical structure of 4,4'-DMAR

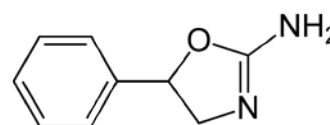


Figure 2: Chemical structure of Aminorex

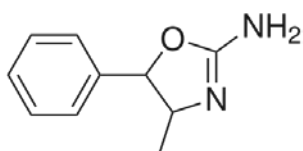


Figure 3: Chemical structure of 4-methylaminorex (4-MAR)

2.2. There are two chiral centres in the oxazoline ring of 4,4'-DMAR and so there are four different enantiomers or two different racemic (\pm)-*cis* and (\pm)-*trans* racemates; the analysis of seized and biological samples suggests that it is the *cis* isomer of 4,4'-DMAR that is available on the drugs market in the UK and elsewhere in Europe [Brandt 2014].

2.3. 4,4'-DMAR is often sold under the name Serotoni, other common names are 4,4'-dimethylaminorex, Direx, 4-methyl-euphoria, 4-methyl-U4Euh and ST60.

3. Availability

- 3.1. 4,4'-DMAR has been detected in tablet and powder form in the UK and a number of other European countries including the Netherlands, Denmark, Finland, France, Sweden, Poland, Romania and Hungary [EMCDDA Europol 2014]. The seizures in the UK that have been reported to the EMCDDA include seizures of tablets in Northern Ireland (labelled "Speckled Cherry" or "Speckled Cross") and white powder in Scotland [EMCDDA Europol 2014]. Analysis of products has shown that 4,4'-DMAR is often the only active substance, but some samples have contained other drugs including mephedrone and synthetic cannabinoids.
- 3.2. An Internet snapshot study undertaken in the UK in April 2014 using EMCDDA methodology only identified one site selling 4,4'-DMAR (in contrast 20 Internet sites selling the controlled substance 4-MAR were identified) [Nizar 2014].
- 3.3. In April 2014 the UK Focal Point reported 2 seizures in Scotland containing 4,4'-DMAR (1.2 grams of white powder within 5 small plastic bags were seized on 13 April 2014 by the Police in Renfrew, Scotland; and trace samples of white powder, seized on 16 April 2014).
- 3.4. In April 2014 the UK Focal Point reported on the analysis of a test purchase from an Internet vendor. The sample which was sold as "4,4'-DMAR" was purchased and characterised by the School of Pharmacy & Biomolecular Sciences (Liverpool John Moores University) and ROAR Forensics (Malvern) in March 2014. This test purchase was confirmed to contain 4,4'-DMAR.
- 3.5. A Drugs Early Warning System (DEWS) survey in October 2014 failed to find any UK-based "Clearnet" websites openly offering 4,4'-DMAR for sale.
- 3.6. Forensic Early Warning System (FEWS) surveys have also failed to detect 4,4'-DMAR in UK samples.

4. Consultation on legitimate uses

- 4.1. The ACMD consulted with the Department for Business Innovation and Skills (BIS) and the Medicines and Healthcare products Regulatory Agency (MHRA) and found no legitimate medicinal, industrial or commercial use for 4,4'-DMAR.

5. Pharmacology

- 5.1. A recent *in vitro* study using rat synaptosomes has shown that *cis*-4,4'-DMAR is a potent releaser of dopamine, norepinephrine and serotonin [Brandt et al 2014]. This study showed that *cis*-4,4'-DMAR has comparable potency to induce release

at the dopamine and norepinephrine transporters and greater potency to induce release at the serotonin transporter than *d*-amphetamine and aminorex (*table 1*).

	DAT (nM)	NET (nM)	SERT (nM)
<i>d</i> -Amphetamine	5.5 ± 0.5	8.2 ± 1.6	2602 ± 494 473
Aminorex	9.1 ± 0.9 1	5.1 ± 3.5	414 ± 78 45
cis-4-MAR c	1.7 ± 0.2	4.8 ± 0.9	53.2 ± 6.8 31
cis-4,4 -DMAR	8.6 ± 1.1	26.9 ± 5.9	18.5 ± 2.8 2

Table 1 - modified from Brandt et al., (2014). DAT: dopamine transporter; NET: norepinephrine transporter; SERT; serotonin transporter; [3H]-1-methyl-4-phenylpyridinium ([3H]MPP+) used as radiolabeled substrate for DAT and NET and [3H]5-HT (serotonin) for SERT. Data expressed as mean ± SD for N = 3–4 experiments performed in triplicate

5.2. There are no data from published studies on the pharmacokinetics including the metabolism of 4,4'-DMAR. Reports on drug user Internet discussion forums suggest an onset of action of 4,4'-DMAR of up to one hour which may lead some users to re-dose; these reports suggest that the effects may last for several hours.

6. Acute Toxicity and Deaths

6.1. There has been one report to the EMCDDA from Poland of a non-fatal intoxication with analytical confirmation of 4,4'-DMAR; limited clinical details were available in this report [EMCDDA Risk Assessment Report].

6.2. There have been 46 deaths associated with 4,4'-DMAR in Europe (37 in the UK, eight in Hungary and one in Poland). Clinical features reported prior to death in these cases included agitation, convulsions and hyperthermia [EMCDDA Risk Assessment Report]. 4,4'-DMAR was detected in post-mortem biological samples in all of these deaths.

6.3. On 12 June 2014 the UK Focal Point reported a death of a 19 year old female on 13 April 2014 in Glasgow. 4,4'-DMAR was confirmed analytically, and no other substances were detected. All of the other deaths reported in the UK were in Northern Ireland. Cosby *et al* (2014) reported on 18 deaths in Northern Ireland between June and December 2013. 4,4'-DMAR was analytically detected in biological samples at concentrations from 0.2 – 3.75 ,mg/L. The Department of Health, Social Services and Public Safety for Northern Ireland (DHSSPSNI) reported similar results on a further 21 inquests held in Northern Ireland for 01 June – 31 July, 2014 (a personal communication from Gary Maxwell, Health Department Policy Branch). 4,4'-DMAR was detected in blood samples at concentrations from 0.2 – 3.73 mg/L. in 18 cases.

6.4. Other drugs were found on analysis of post-mortem samples in all but one of 44 cases. An analysis by the EMCDDA of the 31 deaths reported in 2013 in which 4,4'-DMAR was detected concluded that 4,4'-DMAR was the cause of death in 3 cases and contributed to death in 20 cases even in the presence of other drugs [EMCDDA Risk Assessment Report].

7. Social Harms

7.1. 4,4'-DMAR has only been available in Europe since December 2012 and there have been no studies which have assessed the potential social harms associated with its use.

8. Control

8.1. 4,4'-DMAR is subject to control under drug control legislation in Denmark, Finland and Slovenia. Hungary, Ireland, Poland, Romania and Spain control 4,4'-DMAR using other legislation.

8.2. The EMCDDA/EUROPOL issued a joint report on 4,4'-DMAR in July 2014 and the EMCDDA undertook a formal Risk Assessment of 4,4'-DMAR on 16th September 2014 and this has been submitted to EU Council for approval.

9. Conclusions

9.1. Given that there have been deaths associated with 4,4'-DMAR in the short period of time that it has been available in the UK, the ACMD believes that 4,4'-DMAR should be subject to control in the UK.

10. Recommendation

10.1. The ACMD recommends that 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-DMAR) be controlled as a Class A substance and scheduled under Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended).

References

Brandt SD, Baumann MH, Partilla JS, Kavanagh PV, Power JD, Talbot B, Twamley B, O'Brien J, Mahony O, Elliott SP, Archer RP, Patrick J, Singh K, Dempster NM, Characterization of a novel and potentially lethal designer drug, (+/-)-cis-para-methyl-4-methylaminorex (4,4'-DMAR or 'Serotoni'). *Drug Testing and Analysis*. 2014; 6:684–695.

Cosbey SH, Kirk S, McNaul M , et al . Multiple fatalities involving a new designer drug: para-methyl-4-methylaminorex. *J.Anal Toxicol.*,2014; 38:383-384

EMCDDA, Europol. 2014. EMCDDA–Europol Joint Report on a new psychoactive substance: 4,4'-DMAR (4-methyl-5-(4-methylphenyl)-4,5- dihydrooxazol-2-amine), Joint Reports, Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_229825_EN_TDAS14006ENN.pdf

EMCDDA (2014) Risk assessment report of a new psychoactive substance: 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-DMAR) . Available at: <http://data.consilium.europa.eu/doc/document/ST-13500-2014-INIT/en/pdf>

Nizar H, Dargan PI, Wood DM. 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* 2014 Aug 29 [Epub ahead of print; PMID: 25167967]

Annex 1 – EMCDDA Risk Assessment of 4,4'-DMAR

1. Introduction

This risk assessment report presents the summary findings and the conclusions of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine, commonly known as **4,4'-dimethylaminorex (4,4'-DMAR)**. The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines ⁽¹⁾. It is written as a stand-alone document, which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on 4,4'-DMAR, is provided below.

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ⁽²⁾ (hereafter 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' ⁽³⁾) that may pose public-health and social threats, including the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances ⁽⁴⁾ that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ⁽⁵⁾.

4,4'-DMAR was first detected in a seizure by customs in the Netherlands in December 2012 and formally notified to the Early Warning System in December 2012. Following an assessment of

⁽¹⁾ EMCDDA, (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, Publications Office of the European Union, Luxembourg. Available at: <http://www.emcdda.europa.eu/html.cfm/index100978EN.html>

⁽²⁾ OJL 127, 20.5.2005, p. 32.

⁽³⁾ The information exchange mechanism laid down by the Council Decision is operationalized as the *European Union Early Warning System on New Psychoactive Substances ('Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Reitox National Focal Points in the Member States, the European Commission and the European Medicines Agency.

⁽⁴⁾ According to the definition provided by the Council Decision, a 'new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; 'new narcotic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

⁽⁵⁾ In compliance with the provisions of the 1961 United Nations Single Convention on Narcotic Drugs and the 1971 United Nations Convention on Psychotropic Substances.

the available information on 4,4'-DMAR, and in accordance with Article 5 of the Council Decision, on 8 May 2014 the EMCDDA and Europol submitted to the Council of the European Union, the European Commission and the European Medicines Agency (EMA) a *Joint Report* on 4,4'-DMAR⁽⁶⁾. Taking into account the conclusion of the *Joint Report*, and in accordance with Article 6 of the Council Decision on 20 June 2014, the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of 4,4'-DMAR was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of five additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of 4,4'-DMAR, including health and social risks. Furthermore, two experts from the Commission, one expert from Europol and one expert from the European Medicines Agency (EMA) participated in the risk assessment. The meeting took place on 16 September 2014 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMA. A list of the extended Scientific Committee, as well as the list of participants attending the risk assessment meeting, is annexed to this report (Annex 2).

For the risk assessment, the extended Scientific Committee considered the following information resources:

- i. Technical report on 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-dimethylaminorex, 4,4'-DMAR) (Annex 1);
- ii. EMCDDA–Europol Joint Report on a new psychoactive substance: 4,4'-DMAR (4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine);
- iii. Scientific articles, official reports, grey literature, Internet drug discussion forums and related websites (hereafter 'user websites');
- iv. Data from EMCDDA Internet monitoring of suppliers (that typically appear to be manufacturers and/or wholesalers) and retailers selling 4,4'-DMAR;
- v. Risk assessment of new psychoactive substances: Operating guidelines; and
- vi. Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances.

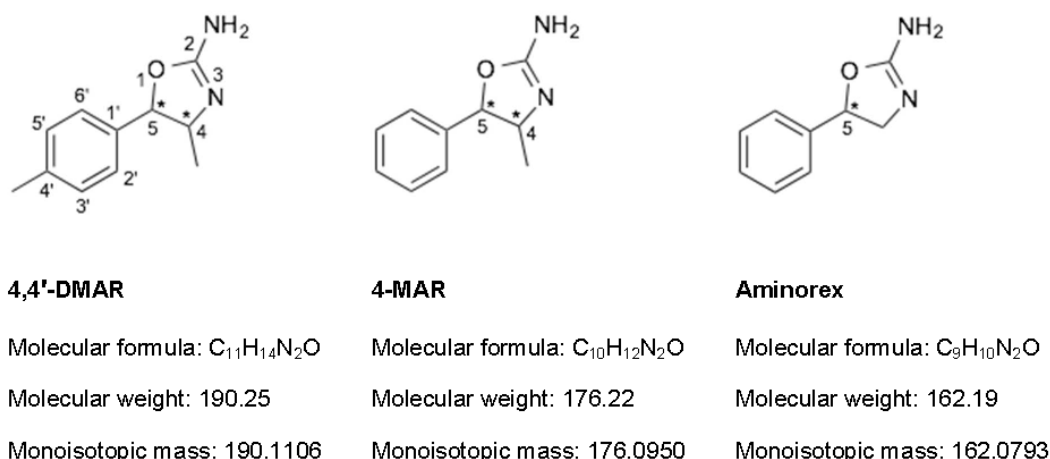
⁽⁶⁾ EMCDDA and Europol (2012), EMCDDA–Europol joint report on a new psychoactive substance: 4,4'-DMAR (4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine), EMCDDA, Lisbon. Available at: <http://www.emcdda.europa.eu/publications/joint-reports/4-4-DMAR>

Finally, it is important to note that this risk assessment report contains a discussion of the available information on non-fatal intoxications and deaths associated with 4,4'-DMAR. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. As a result, more information is available; however, it is likely that serious adverse events remain under-detected.

2. Physical and chemical description of 4,4'-DMAR and its mechanisms of action, including its medical value

4,4'-DMAR is a synthetic substituted oxazoline derivative (Figure 1). 4,4'-DMAR may be considered a derivative of the stimulants aminorex and 4-methylaminorex (4-MAR), which are controlled under the 1971 United Nations Convention on Psychotropic Substances. The systematic (International Union of Pure and Applied Chemistry, IUPAC) name of 4,4'-DMAR is 4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine but other names and abbreviations are used, including *para*-methyl-4-methylaminorex (Annex 1).

Figure 1. The molecular structure, formula, relative molecular weight and monoisotopic mass of 4,4'-DMAR. Structures of 4-MAR and aminorex are provided for comparison. Asterisk indicates chiral carbon.



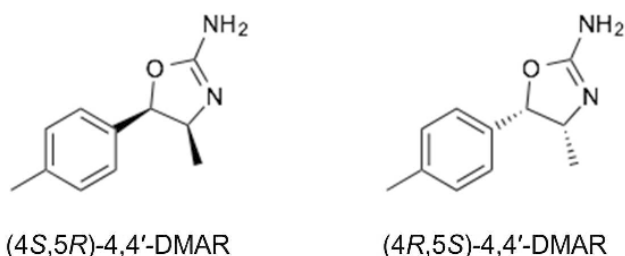
The presence of two chiral centres within the oxazoline ring gives rise to four enantiomers or two (\pm)-*cis* and (\pm)-*trans* racemates which may have different biological properties (Figure 2) ⁽⁷⁾. Due to additional complexities involved in the preparation of these compounds, the enantiopure

⁽⁷⁾ (\pm) denotes the presence of the racemic mixture and will be omitted for clarity in the remaining text when reference is made to either *cis*- or *trans* 4,4'-DMAR instead of (\pm)-*cis*- and (\pm)-*trans*-4,4'-DMAR, respectively.

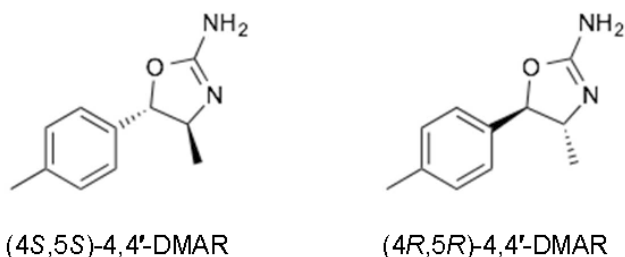
forms seem less likely to appear on the drug market when compared to the racemic *cis*- and *trans* forms.

Detailed information on the analytical profile of 4,4'-DMAR is provided in Annex 1. Briefly, analysis of the compound itself is straightforward (e.g. as a powder or tablet) with suitable equipment but the availability of analytical reference material is important for the correct identification of the *cis*- or *trans* isomeric form. Detection in biological fluids, however may require the implementation of more sensitive techniques coupled with appropriate chromatographic separation. A range of positional isomers are possible and implementation of analytical separation techniques may be used to obtain unambiguous differentiation. No information was provided regarding the possible presence of the other isomers on the drug market. There is no information on presumptive colour tests with 4,4'-DMAR. No immunoassay field test for 4,4'-DMAR is currently available. Analytical reference materials facilitating the quantification of 4,4'-DMAR in biological matrices are available.

Figure 2. Molecular structures of the four possible 4,4'-DMAR enantiomers.



Racemic form: (\pm)-*cis*-4,4'-DMAR or (4/SR/,5/RS/)-4,4'-DMAR



Racemic form: (\pm)-*trans*-4,4'-DMAR or (4/SR/,5/SR/)-4,4'-DMAR

The free base of the *cis*- and *trans* isomers have been described as colourless solids and the hydrochloride salt form is a white powder soluble in water. In cases where sufficient analytical data were available from information provided about detections ⁽⁸⁾, the presence of the *cis*-form

⁽⁸⁾ 'Detections' is an all-encompassing term, which may include seizures and/or collected and/or biological samples. Seizure

was indicated. It is unknown if the *trans*-isomers are also circulating on the drug market.

4,4'-DMAR has typically been seized as white or coloured powders and tablets.

Reported routes of administration for 4,4'-DMAR include nasal insufflation, oral administration, inhalation ('methpipe') and in one of the death cases reported by Hungary, the route of administration was by injection. Information from user websites suggest that a range of doses are used that may depend on the route of administration but single, typical, oral 'doses' between 10–60 mg were noted, but doses up to 200 mg have also been reported.

No data are available on the pharmacokinetics of 4,4'-DMAR, and no metabolites of the substance have been identified.

Data on the pharmacology of 4,4'-DMAR is limited to recent *in vitro* studies examining the monoamine transport/release activity of *cis*- and *trans*-4,4'-DMAR (using rat brain synaptosomes). *cis*-4,4'-DMAR was found to be a potent releaser of dopamine (DA) (EC_{50} 8.6 nM), norepinephrine (NE) (EC_{50} 26.9 nM) and serotonin (5-HT) (EC_{50} 18.5 nM). *d*-Amphetamine (DA: EC_{50} 5.5 nM; NE: 8.2 nM; 5-HT: 2602 nM), aminorex (DA: EC_{50} 9.1 nM; NE: 15.1 nM; 5-HT: 414 nM), and *cis*-4-methylaminorex (DA: EC_{50} 1.7 nM; NE: 4.8 nM; 5-HT: 53.2 nM) were used for comparison.

Further studies with (*S*)-(+)-3,4-methylenedioxymethamphetamine as a comparator (DA: EC_{50} 143 nM; NE: 98.3 nM; 5-HT: 85.0 nM) revealed that both *cis*-4,4'-DMAR (DA: EC_{50} 10.9 nM; NE: 11.8 nM; 5-HT: 17.7 nM) and *trans*-4,4'-DMAR (DA: EC_{50} 24.4 nM; NE: 31.6 nM; 5-HT: 59.9 nM) were more potent catecholamine releasers. Of note, *trans*-4,4'-DMAR appeared to act as an uptake inhibitor rather than a substrate-type serotonin releasing agent.

Knowledge is emerging about the *in vitro* pharmacological properties of 4,4'-DMAR but it is difficult to predict potential drug interactions or contraindications. Briefly, as noted above, the ability of both *cis*- and *trans*-4,4'-DMAR to display potent monoamine transporter activity *in vitro* may be relevant when considering potential interactions with other substances that act on similar targets that affect dopamine, norepinephrine and serotonin levels. For example, the use of substances including medicinal products, known to increase 5-HT-release and/or reuptake (such as selective serotonin reuptake inhibitors (SSRIs), MDMA, mephedrone and cocaine) may increase the risk of developing serotonergic toxicity (often also referred to as serotonin syndrome). High dosage levels and/or combinations of 4,4'-DMAR with other catecholamine releasing agents e.g. amphetamine-type stimulants, may lead to increasing risk of developing psychotic symptoms and agitation, while potentially dangerous cardiovascular effects could be produced by excessive norepinephrine release in the periphery. However, further studies are

means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

warranted to assess these effects in detail.

There are no animal or human study data related to the toxicity, including median lethal dose (LD₅₀), potential for self-administration, nor investigations on psychological and/or behavioural effects of 4,4'-DMAR. Self-reports available on user websites suggest that the effects of 4,4'-DMAR include euphoria, mental and physical stimulation, empathic effects and changes in visual perception.

The synthesis and analytical characterisation of both *cis*- and *trans*-4,4'-DMAR was first published in 2014 and adapted from methods published in the scientific literature on related aminorex derivatives. 4,4'-DMAR is available as an analytical reference standard and for use in scientific research. The (4*S*,5*S*)-*trans*-4,4'-DMAR enantiomer has been featured in several patents related to the preparation of a range of phospholipase A2 inhibitors. There are currently no other indications that 4,4'-DMAR may be used for other legitimate purposes, including as a component in industrial, cosmetic or agricultural products.

4,4'-DMAR has no established or acknowledged medical value or use (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for 4,4'-DMAR in the European Union or in the Member States that responded to the information request by the EMA that was launched under Article 5 of the Council Decision. In addition, there is no information that 4,4'-DMAR is used for the manufacture of a medicinal product or an active pharmaceutical ingredient (API) of a medicinal product in the European Union. It is important to note that the data collection is incomplete and some countries indicated that this information is not known. However, it should be noted that there is no European Union database on the synthetic routes of all registered medicinal products. Therefore, the use of 4,4'-DMAR cannot be ruled out with certainty.

3. Chemical precursors that are used for the manufacture of 4,4'-DMAR

There is currently no information regarding manufacturing sites, the chemical precursors or the synthetic routes used for 4,4'-DMAR that has been detected on the drug market within the European Union. The route(s) employed for the preparation of the collected 4,4'-DMAR samples have not been reported. The method published in the scientific literature used 1-(*p*-tolyl)propan-1-one as the starting point. This chemical is commercially available. Key intermediates included the primary amine normephedrone, which underwent a reduction to yield the 2-amino-1-(*p*-tolyl)propan-1-ol precursor. The cyclisation carried on from that gave the *cis*- and *trans* isomers of 4,4'-DMAR. While it is conceivable that these intermediates may be obtained from alternative routes of synthesis, information about their preparation associated with the seized products is not available. It would be expected that any synthesis would produce some impurities.

4. Health risks associated with 4,4'-DMAR

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of 4,4'-DMAR, as well as its dependence potential, and its similarities to and differences

from other chemically or pharmacologically related substances, such as 4-methylaminorex and aminorex which all share the ability to act as catecholamine releasers (dopamine and noradrenaline).

It is important to note that when interpreting the information from non-fatal intoxications and deaths reported by Member States as well as user websites, individuals may have used other pharmacologically active substances in addition to 4,4'-DMAR. The presence of and/or interaction with other substances may account for some of the reported effects.

The mode of use may involve the combined use (either intentionally or unintentionally) of other drugs, especially when encountered surreptitiously within ecstasy-type tablets or powders offered and disguised in combination with other substances that affect monoaminergic systems. Analysis of various seized products have shown that the composition can differ and the user is unlikely to be aware of the exact dose or compound being ingested (by whatever route) which presents an inherent risk to the individual.

One non-fatal analytically confirmed intoxication has been reported from Poland.

A total of 31 deaths associated with 4,4'-DMAR were reported by Hungary (eight deaths), Poland (1 death) and the United Kingdom (22 deaths). In all these cases 4,4'-DMAR was analytically confirmed. In 23 deaths, 4,4'-DMAR was either the cause of death (3 cases) or is likely to have contributed to death (20 cases) even in the presence of other substances; in 1 of these deaths 4,4'-DMAR was the sole drug present. In 8 deaths, 4,4'-DMAR may have contributed to toxicity but other substances were present that may have been more toxicologically significant. In 27 cases other stimulants (including cocaine, amphetamines and new psychoactive substances such as synthetic cathinones) were found.

Information provided by the Member States related to these deaths noted a number of adverse effects, including: agitation, hyperthermia, convulsions, breathing problems and cardiac arrest.

There is no information on the psychosocial consequences of (chronic) use of 4,4'-DMAR.

No studies have been published on the neurotoxicity, reproductive toxicity, genotoxicity or carcinogenic potential of single or repeated doses of 4,4'-DMAR. No studies have examined the chronic toxicity of 4,4'-DMAR in animals or humans.

Public health risks

The public health risks associated with 4,4'-DMAR may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences. Detailed information, including data on sporadic vs. chronic use that allow for a determination of public health risks associated with 4,4'-DMAR are unavailable.

In some cases, 4,4'-DMAR is being sold and consumed as a substance in its own right including in the form of tablets under the name 'serotoni'. It has also been mis-sold on the illicit market as ecstasy and amphetamines. Similar to other stimulant drugs, users may combine 4,4'-DMAR

with other psychoactive substances (e.g. entactogens, stimulants and/or depressants including alcohol).

In September 2014, EMCDDA monitoring of Internet suppliers and retailers identified one site offering 4,4'-DMAR for sale; further details including the quantities available and price were only available on application to the site. Based on data available from EMCDDA monitoring, the number of Internet shops offering this particular substance has declined. An earlier study undertaken in April 2014 identified one Internet site selling 4,4'-DMAR compared to 20 Internet sites selling 4-MAR.

No information on the purity of 4,4'-DMAR that is present on the drug market has been reported. In most cases, 4,4'-DMAR was reported as the only active substance, although in about 20% of detections, it was found in combination with other substances (predominantly stimulants). In these cases, quantitative analyses were not available.

Since December 2012, when 4,4'-DMAR was first detected in the Netherlands, eight additional Member States have reported detections (Denmark, Finland, Hungary, Poland, Romania, Sweden, France and the United Kingdom).

Where information was available with regards to the death cases, it appears that the users did not intentionally purchase 4,4'-DMAR on the street market but rather ecstasy tablets or powders associated with other stimulant drugs (such as cocaine or mephedrone). The use of these tablets and powders were associated with both home and recreational settings.

Information obtained from user websites suggested that the intentional purchase of 4,4'-DMAR from Internet retailers may have been associated with 'psychonauts' who might have explored this new substance in the home environment (where an individual is on their own or in the company of others).

As noted, the preferred route of administration appears to be oral and nasal. Injection was also reported as the route of administration in one of the deaths. As such, sharing of needles and syringes carries the risk of transmission of blood-borne viruses. There are no prevalence data on the use of 4,4'-DMAR within the European Union or elsewhere but available information from user websites and seizures does not suggest wide use of the substance.

5. Social risks associated with 4,4'-DMAR

There is no information on the social risks associated with 4,4'-DMAR.

There is no information on whether the use of 4,4'-DMAR affects education or career, family or other personal or social relationships, including marginalisation.

Data related to the social risk associated with the distribution and trafficking of 4,4'-DMAR are lacking.

Due to lack of data, it is not possible at this time to estimate whether 4,4'-DMAR is associated with greater healthcare costs than other stimulant drugs.

6. Information on the level of involvement of organised crime and information on seizures and/or detections by the authorities, and the manufacture of 4,4'-DMAR

Limited information has been provided by Member States in relation to the involvement of organised crime in the manufacture or trafficking of 4,4'-DMAR. Only one Member State (Hungary) mentioned that organised crime groups are involved in the trafficking and distribution of 4,4'-DMAR; no other details were provided.

Seized tablets found to contain 4,4'-DMAR showed a range of colours, markings and logos ⁽⁹⁾ consistent with ecstasy tablets, raising the possibility that some of these were designed to be sold as ecstasy on the illicit drug market.

The information about the small-scale production of the related substance 4-MAR in the Netherlands in 2009 associated with a group producing other illicit substances would suggest that the capability to manufacture 4,4'-DMAR may exist within illicit drug-producing criminal groups in the European Union.

The largest seizures of 4,4'-DMAR (22 kg and 70 kg) were reported by the Netherlands. They were seized by Customs and originated from outside the European Union.

7. Information on any assessment of 4,4'-DMAR in the United Nations system

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances. On 5 March 2014, the World Health Organization informed the EMCDDA that 4,4'-DMAR is currently not under assessment and has not been under assessment by the UN system and no such assessment is planned.

8. Description of the control measures that are applicable to 4,4'-DMAR in the Member States

4,4'-DMAR is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs or in the 1971 United Nations Convention on Psychotropic Substances (together 'UN drug conventions').

Three Member States (Denmark, Finland and Slovenia) reported that 4,4'-DMAR is subject to control measures under drug control legislation that is in accordance with the UN drug conventions.

Denmark reported that on 27 May 2014, the Minister signed an Executive Order amending the Executive Order on Euphoriant Substances, which entered into force on 30 May 2014.

⁽⁹⁾ It is common to find markings on tablets sold as ecstasy including those of popular cultural and iconic brands often having an association with quality.

Subsequently, the mentioned substances may only be used for medical or scientific purposes.

Finland reported that 4,4'-DMAR was controlled by an Amendment to Government Decree 543/2008, in effect from 4th August 2014.

Slovenia reported that 4,4'-DMAR is included in the Decree on the scheduling of illicit drugs (Official Gazette RS, No. 45/2014) since July 2014.

The remaining 25 Member States, Turkey and Norway do not control 4,4'-DMAR under drug control legislation that is in accordance with the UN drug conventions. Of these, five Member States (Hungary, Ireland, Poland, Romania, Spain) and Norway reported that 4,4'-DMAR is controlled by other legislative measures. In Hungary, 4,4'-DMAR is specifically named in Schedule C of Government Decree 66/2012 (added by '256/2013 (July 5) Government Regulation § 17, Annex 9', effective 15 July 2013). Ireland, Poland and Romania have legislation that prohibits the unauthorised supply of any psychoactive substance that qualifies by conforming to certain criteria. It was reported that national authorities may find that 4,4'-DMAR meets such criteria. Poland reported that 4,4'-DMAR falls under the definition of a 'substitution drug' under the Act amending the Act on Counteracting Drug Addiction and the Act on State Sanitary Inspection, 2010; as such, its marketing and production may be subject to an administrative fine.

Spain reported that 'although there is no current specific legislation, to our knowledge, controlling production, commerce, imports, exports or use/consumption of this substance and given that it may cause harmful effects to those using it, the same way as illegal drugs do, there is generic legislation (administrative and criminal) on health protection which is fully applicable, if necessary'.

Norway reported that 4,4'-DMAR is subject to control measures under medicines legislation.

Twenty Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Estonia, France, Germany, Greece, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Portugal, Slovakia, Sweden and the United Kingdom) and Turkey reported that 4,4'-DMAR is not subject to control measures at the national level.

9. Options for control and the possible consequences of the control measures

Under Article 9.1 of the Council Decision, the option for control that is available at European Union level is for the Member States to submit the new psychoactive substance 4,4'-DMAR to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the UN drug conventions. There are no studies on the possible consequences of such control measures on 4,4'-DMAR. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of 4,4'-DMAR and hence the further expansion of the current open trade in this substance.

- A health consequence that might result from this control option is the benefit brought about by the presumed reduction in availability and use.
- This control option could facilitate the detection, seizure and monitoring of 4,4'-DMAR related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies across the European Union.
- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement and the courts.
- This control option could lead to replacement with other (established or new) psychoactive substances, which may in themselves have public health consequences.
- It is difficult to predict the impact of this control option on current or future research by the pharmaceutical or chemical industries.
- This control option could create an illicit market in 4,4'-DMAR with the increased risk of associated criminal activity, including organised crime. This could include covert sales of 4,4'-DMAR on the Internet or in bricks and mortar headshops.
- This control option could impact on both the quality/purity and price of any 4,4'-DMAR still available on the illicit market. The extent to which this will impact on public health, criminality or levels of use is difficult to predict.

In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of 4,4'-DMAR on the market post-control, should this control option be pursued.

Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include restricting the importation and supply of the substance as some other Member States (and Norway) have already done.

10. Conclusion

The new psychoactive substance 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-DMAR) appears to have psychostimulant properties. It has been available on the drug market in the European Union since at least December 2012. 4,4'-DMAR is structurally related to 4-methylaminorex (4-MAR) and aminorex, which are both listed in the 1971 United Nations Convention on Psychotropic Substances.

4,4'-DMAR can exist in the form of racemic *cis*- and *trans*-4,4'-DMAR. Where isomeric differentiation has been reported, only the *cis*-isomer has been detected. The potential presence of the *trans*-form on the drug market cannot be excluded.

Data on the pharmacology of 4,4'-DMAR is limited to *in vitro* studies. *cis*-4,4'-DMAR is a potent efficacious substrate-type releaser at DAT, NET and SERT in rat brain tissue with comparable potency at DAT and NET to that of *d*-amphetamine and aminorex. On the other hand, *cis*-4,4'-

DMAR exerted much more potent actions at SERT when compared to *d*-amphetamine, aminorex and *cis*-4-MAR. *trans*-4,4'-DMAR was also found to be a non-selective catecholamine releaser but serotonin uptake inhibitor. Both *cis*- and *trans*-4,4'-DMAR were more potent than (S)-(+)-MDMA in its ability to evoke catecholamine release.

There are no data on the dependence potential and abuse liability of 4,4'-DMAR. Although the information available does not suggest it has been widely used, it has been associated with 31 deaths over a period of approximately one year. This raises the concern that if this substance were to become more widely available and used, the implications for public health could be significant.

The pharmacological and behavioural activities of 4,4'-DMAR in humans have not been studied.

4,4'-DMAR has no established or acknowledged medical use (human or veterinary) in the European Union. There are no indications that 4,4'-DMAR may be used for any other purpose, aside from as an analytical reference standard and in scientific research.

4,4'-DMAR emerged on the new psychoactive substances market where it was sold as a 'research chemical' by Internet retailers, but recent data suggest this is no longer the case. In addition, it has also been detected in tablets and powders which are sold on the street market. In about 20% of detections it was found in combination with other psychoactive substances (predominantly stimulants). 4,4'-DMAR has been detected in nine Member States.

One non-fatal intoxication and a total of 31 deaths associated with 4,4'-DMAR have been reported, all of which were analytically confirmed. In 23 deaths, 4,4'-DMAR was either the cause of death or is likely to have contributed to death (even in presence of other substances); in 1 of these deaths 4,4'-DMAR was the sole drug present. In 8 deaths, 4,4'-DMAR may have contributed to toxicity but other substances were present that may have been more toxicologically significant. In 27 cases other stimulants (including cocaine, amphetamines and new psychoactive substances such as synthetic cathinones) were found. Information provided by the Member States related to these deaths noted a number of adverse effects, including: agitation, hyperthermia, convulsions, breathing problems and cardiac arrest.

There are no prevalence data on the use of 4,4'-DMAR. Information from the deaths suggest that users unknowingly consumed 4,4'-DMAR as a result of seeking illicit substances such as ecstasy, cathinones and cocaine. There is no specific information on the social risks that may be related to 4,4'-DMAR.

There is limited information to suggest the potential involvement of organised crime in the manufacture, distribution (trafficking) and supply within the European Union. The chemical precursors and the synthetic routes used to manufacture the 4,4'-DMAR detected within the European Union are unknown.

4,4'-DMAR is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs or in the 1971 United Nations Convention on Psychotropic Substances. 4,4'-DMAR is not undergoing assessment by the United Nations system. Three Member States control 4,4'-DMAR

under drug control legislation and five Member States control 4,4'-DMAR under other legislation.

Many of the questions posed by the lack of data on the risks to individual health, and the absence of data on public health and social risks of 4,4'-DMAR, as for any new psychoactive substance, could be answered through further research. Areas where additional information would be important include: prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); market studies; chemical profiling studies; receptor binding and functional activity studies; metabolic pathway studies; behavioural studies; clinical patterns of acute and chronic toxicity in humans; the potential interaction between 4,4'-DMAR and other substances (in particular those that affect the monoaminergic system); the dependence and abuse potential; and, the social risks associated with its use.

The Committee notes that a decision to control 4,4'-DMAR has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks and consequences arising from the use of 4,4'-DMAR. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Although there is limited information on the human (psycho)pharmacological effects, the emergence of chemically analogous substances to replace 4,4'-DMAR is a possibility. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Finally, control measures should not inhibit the gathering and dissemination of accurate information on 4,4'-DMAR to users, practitioners and decision makers.