



European Monitoring Centre
for Drugs and Drug Addiction

JOINT REPORTS

ISSN 1977-7868

4,4'-DMAR

EMCDDA–Europol Joint Report on a new psychoactive substance: 4,4'-DMAR (4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine)

In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

About this series

EMCDDA–Europol Joint Report publications examine the detailed information provided by the EU Member States on individual new psychoactive substances. Information is collected from the Reitox network, the Europol national units and the national competent authorities of the European Medicines Agency.

Each Joint Report serves as the basis upon which the decision to conduct a risk assessment of the new psychoactive substance is taken. It is part of the three-step procedure involving information exchange, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

Contents

3	1. Introduction
3	2. Information collection process
4	3. Information required by Article 5.2 of the Council Decision
4	3.1. Chemical and physical description, including the names under which the new psychoactive substance is known — Article 5.2(a) of the Council Decision
5	3.2. Information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance — Article 5.2(b) of the Council Decision
5	3.2.1. Information provided to Europol
6	3.2.2. Information provided to the EMCDDA
7	3.3. Information on the involvement of organised crime in the manufacture or trafficking of the new psychoactive substance — Article 5.2(c) of the Council Decision
7	3.4. A first indication of the risks associated with the new psychoactive substance, including the health and social risks, and of the characteristics of users — Article 5.2(d) of the Council Decision
7	3.4.1. First indication of health risks
9	3.4.2. Characteristics of users
10	3.5. Information on whether or not the new substance is currently under assessment, or has been under assessment, by the UN system — Article 5.2(e) of the Council Decision
10	3.6. The date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol — Article 5.2(f) of the Council Decision
10	3.7. Information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State — Article 5.2(g) of the Council Decision
11	3.8. Further information — Article 5.2(h) of the Council Decision
11	3.8.1. The chemical precursors that are known to have been used for the manufacture of the substance
11	3.8.2. The mode and scope of the established or expected use of the new substance
11	3.8.3. Other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks
11	4. Information from the EMA as requested by Article 5.3 of the Council Decision
11	4.1. Marketing authorisation
12	4.2. Application for a marketing authorisation
12	4.3. Suspended marketing authorisation
12	5. Conclusion
13	References
14	Annexes

Acknowledgements

The EMCDDA would like to thank the following for their contribution in producing this publication:

- | the Early Warning System (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
- | the Europol national units (ENUs) and Europol Project Synergy;
- | the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway and Iceland;
- | the European Medicines Agency (EMA) and the European Commission;
- | the World Health Organization;
- | Dr Simon Brandt and colleagues for providing data on the pharmacology of 4,4'-DMAR.

Project team: Andrew Cunningham, Michael Evans-Brown, Ana Gallegos, Roumen Sedefov, Anabela Almeida (EMCDDA) and Daniel Dudek (Europol).

1. Introduction

Article 5.1 of Council Decision 2005/387/JHA ⁽¹⁾ (hereinafter referred to as 'the Council Decision') stipulates that '*Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report (hereinafter the "Joint Report").*' The Joint Report shall be submitted to the Council, the European Medicines Agency (EMA) and the European Commission.

In February 2014 the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol examined the available information on a new psychoactive substance, 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine, commonly known by the abbreviation 4,4'-DMAR ⁽²⁾, through a joint assessment based upon the following criteria:

1. the amount of the material seized;
2. evidence of organised crime involvement;
3. evidence of international trafficking;
4. analogy with better-studied compounds;
5. evidence of the potential for further (rapid) spread; and,
6. evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information collected on 4,4'-DMAR satisfied criteria 4, 5 and 6. The two organisations therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on 4,4'-DMAR as stipulated by Article 5.1 of the Council Decision.

2. Information collection process

In compliance with the provisions of the Council Decision, on 27 February 2014 the EMCDDA and Europol launched a procedure for the collection of information on 4,4'-DMAR, in order to prepare the Joint Report. The information was collected mainly through the Reitox national focal points in the Member States, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland and Liechtenstein. The information collection process was largely concluded by 11 April 2014; additional information and clarifications from some countries were received up to four weeks after this date.

Europol asked the Europol National Units to provide information on:

- the level of 4,4'-DMAR production in their country;
- the level of 4,4'-DMAR distribution in their country;
- the level of 4,4'-DMAR trafficking in their country, for internal, transit or export purposes;
- the number of seizures of 4,4'-DMAR in their country, the total amount of the seizures, country of origin, details on the physical forms (including photos);
- the role of organised crime, or criminal groups, in the production, distribution and trafficking of 4,4'-DMAR in their country; and,
- any known aspect of violence and/or money laundering relating to the production and trafficking of 4,4'-DMAR.

Europol received responses from 22 Member States.

According to Article 5.3 of the Council Decision, the EMA requested the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland and Liechtenstein to provide information on whether:

- the new psychoactive substance 4,4'-DMAR has obtained a marketing authorisation;
- the new psychoactive substance 4,4'-DMAR is the subject of an application for a marketing authorisation; and,
- a marketing authorisation that had been granted in respect of the new psychoactive substance 4,4'-DMAR has been suspended.

The EMA received responses from 21 Member States ⁽³⁾, Norway and Iceland. The EMA also provided information as relevant to the central authorisation procedure.

Furthermore, in anticipation of Article 7.3 of the Council Decision in relation to the manufacturing of medicinal products in the European Union, the EMA also requested information on whether the new psychoactive substance 4,4'-DMAR is used to manufacture a medicinal product:

- which has been granted a marketing authorisation;
- for which an application has been made for a marketing authorisation; and,
- for which a marketing authorisation has been suspended by a competent authority.

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

⁽²⁾ 4,4'-DMAR is an abbreviation of 4,4'-dimethylaminorex.

⁽³⁾ Austria, Belgium, Croatia, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, the Netherlands, Poland, Portugal, Slovenia, Spain, Sweden and the United Kingdom.

The EMA received responses from 21 Member States (3), Norway and Iceland. The EMA also provided information as relevant to the central authorisation procedure.

The EMCDDA collected data through:

1. a structured questionnaire from the Reitox national focal points. The EMCDDA received replies from all Member States, Turkey and Norway;
2. data previously provided to the European Union Early Warning System (hereafter 'Early Warning System') through EMCDDA–Europol Reporting Forms, EWS Progress and Final Reports;
3. a specific information request to the World Health Organization on whether or not 4,4'-DMAR is under assessment by the United Nations system (see section 3.5);
4. a structured search of the medical and scientific literature (hereafter 'literature') and Internet suppliers/retailers of new psychoactive substances;
5. a search of relevant Internet drug discussion forums and related websites (hereafter, 'user websites').

Thus, information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part). The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. The conclusion of the Joint Report was prepared and agreed by the two organisations responsible — the EMCDDA and Europol. Further details of the seizures and collected samples (including images where available) reported

to the EMCDDA and Europol are provided in Annex 1. The details of deaths associated with 4,4'-DMAR that have been reported to the EMCDDA are provided in Annex 2.

3. Information required by Article 5.2 of the Council Decision

The order and titles of subsections 3.1 to 3.8 and section 4 below are as they appear in Article 5.2(a) to (h) and Article 5.3(a) to (c) of the Council Decision; all sections are cross-referenced with those set down in the Council Decision.

3.1. Chemical and physical description, including the names under which the new psychoactive substance is known — Article 5.2(a) of the Council Decision

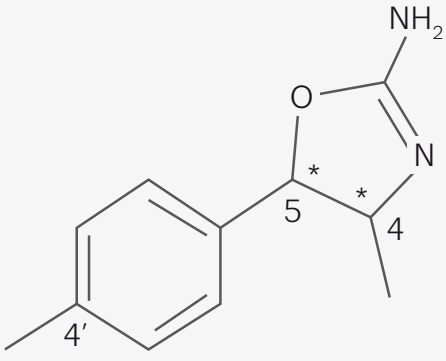
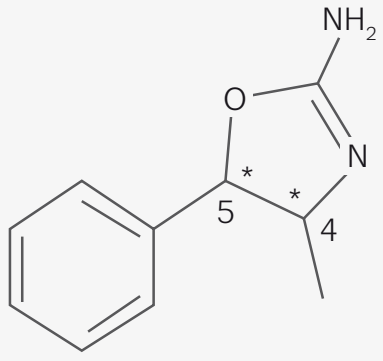
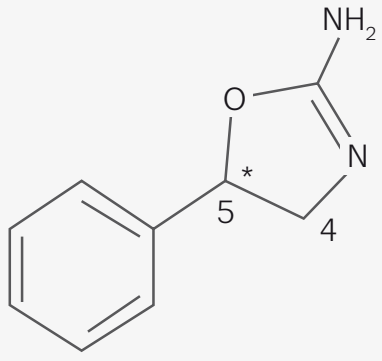
Chemical description and names

4,4'-DMAR is a di-substituted 2-amino-5-phenyl oxazoline substance, substituted with a methyl group both at the 4 position on the phenyl ring and the oxazoline ring. It is a derivative of aminorex and 4-methylaminorex (4-MAR), both synthetic stimulants which are controlled under the 1971 United Nations Convention on Psychotropic Substances; 4-MAR is listed in Schedule I and aminorex is listed in Schedule IV. The structures of 4,4'-DMAR, 4-MAR and aminorex are provided in Figure 1.

FIGURE 1

The numbered molecular structure, formula, weight and monoisotopic mass of 4,4'-DMAR.

The molecular structures of 4-MAR and aminorex are provided for comparison.

		
4,4'-DMAR	4-MAR	Aminorex
Molecular formula: C ₁₁ H ₁₄ N ₂ O Molecular weight: 190.24 Monoisotopic mass: 190.111		

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

Additional chemical names have been reported:

4,5-dihydro-4-methyl-5-(4-methylphenyl)-2-oxazolamine
4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine

Common names or codenames have also been reported:

para-methyl-4-methylaminorex;
p-methyl-4-methylaminorex;
4-methylaminorex p-methyl derivative;
4,4'-dimethylaminorex;
p4-DMAR;
4-methyl-euphoria;
4-methyl-U4Euh;
4-M-4-MAR;
Serotoni;
ST.

The 'euphoria' or 'U4Euh' component of these names refers to a slang term for the stimulant 4-MAR (Figure 1), which was a 'designer drug' that appeared in the 1980s as a street drug (Davis et al., 1988; Klein et al., 1989).

Chemical Abstract Service (CAS) registry numbers

1445569-01-6 form not specified
364064-08-4 free base of the (4S,5S)-enantiomer

No further CAS registry numbers were identified at this stage.

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS registry numbers listed above. The search returned no results.

Physical description

The hydrochloride salt form of 4,4'-DMAR is a crystalline solid at room temperature.

Information provided from seizures and a collected sample have noted the presence of 4,4'-DMAR in powders and tablets.

The (±)-*cis* racemate was characterised in the collected sample that was reported by the United Kingdom. No information was provided on the chemical form present in the other detections of the substance reported by the Member States.

A more detailed description of 4,4'-DMAR seizures and collected samples encountered can be found in subsections

3.2.1 and 3.2.2 below. Images of seizures and collected samples are provided in Annex 1.

3.2. Information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance — Article 5.2(b) of the Council Decision

3.2.1. Information provided to Europol

Europol received replies from 22 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden). Of these, 18 countries had no data relating to 4,4'-DMAR (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Estonia, France, Germany, Italy, Latvia, Lithuania, Luxembourg, Portugal, Slovakia, Slovenia, Spain and Sweden). The remaining four countries (Finland, Hungary, the Netherlands and Romania) reported the following information.

The level of production, distribution and trafficking

Finland reported a small seizure that took place on 23 May 2013. It was a confiscation of two tablets containing 4,4'-DMAR, made by customs authorities in Helsinki, in a parcel coming from the United Kingdom. This seizure was reported by the Finnish national focal point to the EMCDDA on 2 July 2013 (see section 3.2.2 below).

Hungary reported that 4,4'-DMAR had been used to make tablets, and that this tableting was presumably done in Hungary. No further details were provided.

Hungary provided data revealing a significant number of seizures where 4,4'-DMAR had been identified. According to this information, between June and October 2013 the Hungarian authorities recorded 78 seizures of 4,4'-DMAR. The Hungarian national focal point also reported these seizures to the EMCDDA (see section 3.2.2 below). This is a clear indication of the wide availability of this substance in the Hungarian drug market. According to the Hungarian information, the substance was mainly shipped from China. In a significant majority of the recorded seizures, 4,4'-DMAR was identified on its own. There have been also seizures, both in powder and tablet form, when the substance was seized as a mixture with other new psychoactive substances (predominantly cathinones) such as pentedrone, methcathinone, MPPP, alpha-PVP, bk-MPA, PVP and

mephedrone, and also in combination with UR-144, RH-34 and 5-APDB.

As already mentioned, 4,4'-DMAR was seized either in powder or in tablet form. Seizures in powder ranged from 0.01 g to 192.87 g. In the majority of cases, the powder was white; however, pink, green and blue powder has also been reported. In relation to tablets, they have been reported in different colours and as specific shapes or specific pressed logos, such as: 'Playboy', 'Heart', 'Mitsubishi', 'Star' and 'Transformers' (see Annex 1). According to Hungarian authorities, the number of seizures related to 4,4'-DMAR significantly decreased after the introduction of control measures.

The Netherlands reported only one incident where 4,4'-DMAR was detected. It was a shipment of a parcel containing 500 g of pale yellow powder. The package was sent from India and was destined for a well-known wholesaler of new psychoactive substances in the Netherlands. On the shipping documents, the substance was declared as: 4,5-DYHYDRO-4-METHYL-5-(4-METHYLPHENYL)-2-OXAZOLAM (the correct chemical name for 4,4'-DMAR, apart from the three missing final letters 'INE'). Due to current legislation in the Netherlands, it is not possible to seize new psychoactive substances that are not controlled. The Netherlands national focal point reported this detection to the EMCDDA on 10 December 2012 (see section 3.2.2 below).

Romania reported 14 seizures where 4,4'-DMAR was identified. In 13 cases the substance was seized as white powder totalling 564.23 g. In the other incident five tablets containing 4,4'-DMAR were seized. It was also stated that in all cases the substance was shipped from abroad and intended for so-called 'own consumption'. No further details were provided. The Romanian national focal point also reported 13 of these seizures to the EMCDDA (see section 3.2.2 below).

No reports were received that indicated licit or illicit production of 4,4'-DMAR in any Member States. However, the Netherlands reported an incident from 2009 related to the production of 4-MAR, which is closely related to 4,4'-DMAR. The case involved the discovery of an illicit production site. The forensic examination conducted by the Netherlands Forensic Institute demonstrated that both MDMA via the bromosafrole route and PMK⁽⁴⁾ via the Wacker method were produced in this illicit laboratory. Moreover, several different types of substances, chemicals and recipes were found. It was suggested that it was a so-called 'experimental type' illicit laboratory. Two white plastic trays were found containing a few hundred grams of white powder, which was found to be 4-MAR. Moreover, according to the forensic examination the 4-MAR was illicitly produced at the site. While not related to

4,4'-DMAR, this case would suggest that the capability to manufacture 4,4'-DMAR may exist within drug-producing criminal groups within the European Union.

3.2.2. Information provided to the EMCDDA

The EMCDDA received responses from the 28 Member States, Turkey and Norway. Of these, seven Member States (Denmark, Finland, Hungary, the Netherlands, Romania, Sweden and the United Kingdom) reported detections of 4,4'-DMAR⁽⁵⁾.

Seizures

Seven Member States (Denmark, Finland, Hungary, the Netherlands, Romania, Sweden and the United Kingdom) reported seizures of 4,4'-DMAR.

4,4'-DMAR has typically been seized as powders or tablets. In most cases, 4,4'-DMAR was reported as the only active substance; in about 20 % of detections it was found in combination with other substances. Hungary reported the majority of seizures (78 cases). While the remaining Member States reported a small number of seizures, it is worth noting that in the case of the Netherlands these totalled more than 260 kg of powder. Sweden and Denmark reported that 4,4'-DMAR was detected in seizures of pink/red/purple octagonal tablets bearing the markings 'ST' on one side and '60' on the other. According to user websites, the 'ST' refers to 'Serotoni' and '60' refers to a 60 mg dose.

Denmark reported a seizure by customs of two purple octagonal tablets bearing the markings 'ST/60' in May 2013.

Finland reported a seizure by customs of two red tablets in May 2013.

Hungary reported a total of 78 seizures, which were made by police between June and October 2013. 4,4'-DMAR was seized as tablets (41 seizures) and in powder form (37 seizures). The quantities of tablets seized ranged from a single tablet to 900 tablets, with three seizures above 100 tablets and a total of 1 852 tablets seized. The quantities of powder seized ranged from 0.01 g to 193 g, with 27 seizures below 1 g and a total weight of 337 g seized. In most cases, 4,4'-DMAR was reported as the only active substance; in about 20 % of detections it was found in combination with other substances (predominantly stimulants), including pentedrone (eight cases,

⁽⁵⁾ 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure 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 collected from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).

⁽⁴⁾ Piperonyl methyl ketone, or 3,4-methylenedioxyphenylpropan-2-one.

two of which also contained PVP or alpha-PVP) and mephedrone (one case), RH-34 (two cases), 5-APDB (one case), bk-MPA (one case), ethylphenidate (one case), the synthetic cannabinoid receptor agonist UR-144 (one case) and the common cutting agent creatine monohydrate (one case). In a separate case, 4,4'-DMAR was found in combination with four cathinones (methcathinone, MPPP, pentedrone and alpha-PVP). No quantitative analyses were available.

The Netherlands reported the first seizure of 4,4'-DMAR in November 2012 — the Dutch customs seized 500 g of white powder on 19 November. It was noted that the seizure had arrived from India. This seizure formed the basis of the first notification of detection of 4,4'-DMAR in the European Union (see section 3.6). During 2013 customs authorities in the Netherlands detected a further 260 kg of 4,4'-DMAR; further details are awaited regarding these cases.

Romania reported 13 seizures made by the police in 2013 — as tablets (one case of five tablets) and in powder form (12 cases amounting to a total of 558.84 g).

Sweden reported two seizures made by customs between June and December 2013 — a seizure of 10 g of white powder, and a seizure of two (red or red/pink) octagonal tablets bearing the markings 'ST' on one side and '60' on the other.

The United Kingdom reported four seizures made by police in Northern Ireland, amounting to 447 tablets. In addition, five plastic bags containing white powder (a total amount of approximately 1.2 g) were recovered by police in Scotland in April 2014 during the investigation of a death related to 4,4'-DMAR.

Biological samples

Two Member States (Hungary and the United Kingdom) reported detections of 4,4'-DMAR in biological samples. Twenty-seven deaths (eight in Hungary; 19 in the United Kingdom) were reported. Further details are provided in section 3.4.1 and Annex 2. Hungary also reported the detection of 4,4'-DMAR in biological samples taken in 18 criminal cases related to the consumption of narcotics.

Collected samples

The United Kingdom reported the detection of 4,4'-DMAR in a collected sample. The sample was purchased for GBP 60 (EUR 73) from an Internet retailer (<https://www.chems-direct.org>) in March 2014. The product was a white powder and labelled '5 g' '4,4'-DMAR' (Annex 1). The *cis*-racemate of 4,4'-DMAR was confirmed by NMR and was further characterised. No other substances were reported to be present.

3.3. Information on the involvement of organised crime in the manufacture or trafficking of the new psychoactive substance — Article 5.2(c) of the Council Decision

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.

According to the Hungarian authorities, organised crime groups are involved in the trafficking and distribution of 4,4'-DMAR; no other details were provided.

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

Money laundering aspects

No information was received on money laundering connected to the production and/or trafficking of 4,4'-DMAR.

Violence in connection with production, wholesale and distribution

No information was received on incidents of violence in connection with the production, wholesale and/or trafficking of 4,4'-DMAR.

3.4. A first indication of the risks associated with the new psychoactive substance, including the health and social risks, and of the characteristics of users — Article 5.2(d) of the Council Decision

3.4.1. First indication of health risks

No non-fatal intoxications associated with 4,4'-DMAR were reported by the Member States. A total of 27 deaths associated with 4,4'-DMAR were reported by Hungary (eight deaths) and the United Kingdom (19 deaths). The deaths in Hungary occurred between June and October 2013 and those in the United Kingdom between June 2013 and February 2014. The cause of death has not yet been reported for any of the deaths. Annex 2 provides the available details on these deaths.

Data on gender and age were available for 26 of the decedents. Nineteen were male (four from Hungary; 15 from the United Kingdom); seven were female (four from Hungary; three from the United Kingdom). They were aged between 16 and 43 years.

4,4'-DMAR was detected in post-mortem biological samples in all of the 27 deaths. 4,4'-DMAR was quantified in 23 of the deaths, with concentrations ranging from less than 0.02 mg/L to 3.75 mg/L in blood, and from 5.93 mg/L to 32.95 mg/L in urine. In all of the 27 deaths, one or more psychoactive substances (and/or their metabolites) were detected in post-mortem biological samples in addition to 4,4'-DMAR (Annex 2).

Pharmacology

One study, which the authors provided to the EMCDDA ahead of print, has examined the pharmacology of 4,4'-DMAR. The study examined the effects of (\pm)-*cis*-4,4'-DMAR *in vitro* on effecting release of dopamine, noradrenaline and serotonin at the dopamine transporter (DAT), noradrenaline transporter (NET) and serotonin transporter (SERT), respectively, using rat brain synaptosomes. The effects of (\pm)-*cis*-4,4'-DMAR were compared with *d*-amphetamine, aminorex and (\pm)-*cis*-4-MAR.

The dose-response effects of *d*-amphetamine, aminorex, (\pm)-*cis*-4-MAR and (\pm)-*cis*-4,4'-DMAR on release at DAT, NET and SERT are shown in Figure 2. Potency values (expressed as half maximal effective concentrations, EC₅₀) for the test substances based on data from Figure 2 are provided in Table

1. All four test substances displayed potent releasing activity at DAT, with EC₅₀ values ranging from 1.7 \pm 0.2 nM for (\pm)-*cis*-4-MAR to 9.1 \pm 0.9 nM for aminorex. The drugs also showed considerable potency at NET, with EC₅₀ values ranging from 4.8 \pm 0.9 nM for (\pm)-*cis*-4-MAR to 26.9 \pm 5.9 nM for (\pm)-*cis*-4,4'-DMAR. Activity at SERT varied more than 100-fold across the four substances, with (\pm)-*cis*-4,4'-DMAR exhibiting the highest potency at releasing serotonin (EC₅₀ = 18.5 \pm 2.8 nM). All test substances achieved 100 % of maximal release at DAT, NET and SERT. When considering the overall transporter selectivity of the test compounds, *d*-amphetamine was the most selective for DAT/NET over SERT, with a DAT/SERT ratio of 473, whereas (\pm)-*cis*-4,4'-DMAR was essentially non-selective with a DAT/SERT ratio of 2 (Table 1).

These results suggest that (\pm)-*cis*-4,4'-DMAR is a potent efficacious releaser at DAT, NET and SERT in rat brain tissue. The potency of (\pm)-*cis*-4,4'-DMAR at DAT and NET is similar to that of *d*-amphetamine and aminorex. However, (\pm)-*cis*-4,4'-DMAR exerted much more potent actions at SERT when compared to *d*-amphetamine, aminorex and (\pm)-*cis*-4-MAR (Brandt et al., 2014).

No studies were identified in the literature that have examined the pharmacology of (\pm)-*trans*-4,4'-DMAR.

FIGURE 2

Dose-response effects of *d*-amphetamine, aminorex, (\pm)-*cis*-4-MAR and (\pm)-*cis*-4,4'-DMAR in evoking release from DAT, NET and SERT in rat brain synaptosomes. (\pm)-*cis*-4,4'-DMAR elicited potent release of dopamine, noradrenaline and serotonin.

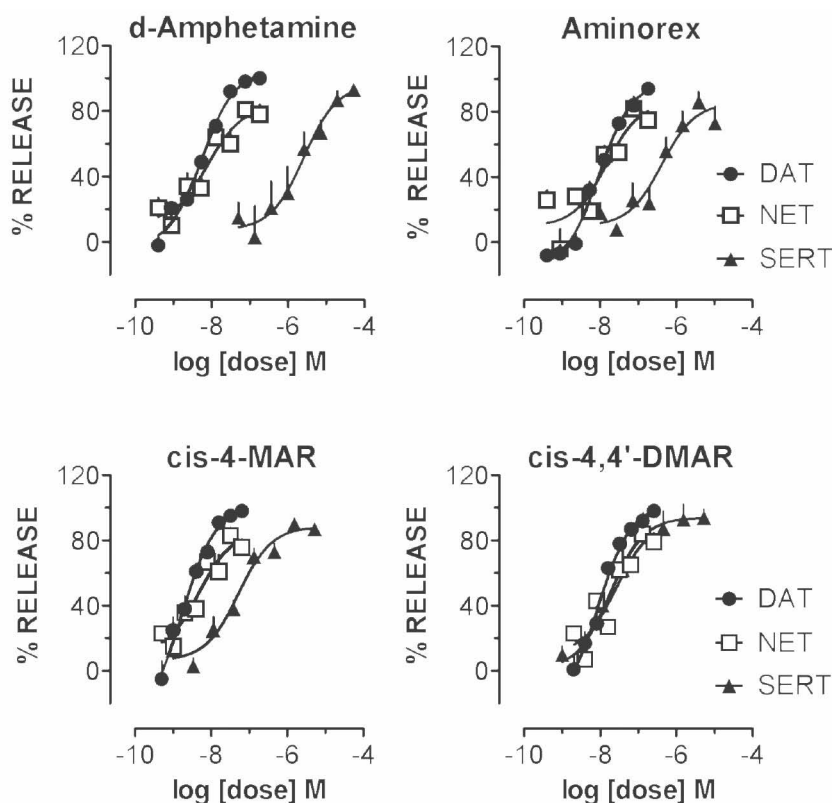


TABLE 1
Stimulation of release at DAT, NET and SERT in rat brain synaptosomes (Brandt et al., 2014).

Substance	Release at DAT EC ₅₀ (nM) ^a	Release at NET EC ₅₀ (nM) ^a	Release at SERT EC ₅₀ (nM) ^a	DAT/ SERT ratio ^b
d-Amphetamine	5.5 ± 0.5	8.2 ± 1.6	2602 ± 494	473
Aminorex	9.1 ± 0.9	15.1 ± 3.5	414 ± 78	45
(±)-cis-4-MAR	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

^a Data are expressed as mean ± SD for n = 3–4 experiments performed in triplicate.

^b DAT/SERT ratio calculated by (EC₅₀ at DAT)⁻¹ / (EC₅₀ at SERT)⁻¹; higher value indicates greater DAT selectivity.

Toxicology

No studies were identified in the literature that have examined the toxicology of 4,4'-DMAR. No clinical case reports related to 4,4'-DMAR toxicity were identified in the literature.

The available information from the 27 deaths reported by Hungary and the United Kingdom is provided in Annex 2. There is insufficient information currently available to characterise the toxidrome related to 4,4'-DMAR exposure.

As discussed above, (±)-cis-4,4'-DMAR has been shown *in vitro* to be a potent substrate-type releaser at DAT, NET, and SERT (Brandt et al., 2014). Based on these data, one hypothesis that requires testing is that (±)-cis-4,4'-DMAR exposure also leads to high levels of extracellular monoamines *in vivo*. Should this be the case, it may explain some of the toxicological features and findings noted in the deaths reported by Hungary and the United Kingdom. In addition, it would also be important to consider potential interactions with other pharmacologically active substances, particularly those that affect the monoaminergic system (Brandt et al., 2014); in this respect it is important to note that in the majority of deaths reported, one or more substances (or their metabolites) known to affect the monoaminergic system — such as cocaine, MDMA, amphetamine — were also detected post-mortem (Annex 2).

Abuse liability and dependence potential

No studies were identified in the literature that have examined the abuse liability and dependence potential of 4,4'-DMAR.

3.4.2. Characteristics of users

No studies were identified that examined the characteristics of users of 4,4'-DMAR. The section below includes a

discussion of the characteristics of users, which includes information from the Member States and self-reported experiences on user websites. Regarding information from user websites, it is important to note that it is not possible to confirm the specific substance(s) used, nor the purity, dose, etc. In addition, analysis of products containing new psychoactive substances that are sold on the drug market has shown that the composition can differ between that claimed by the retailer, and over different geographical areas and time.

Information from seizures, the collected sample, EMCDDA monitoring of Internet suppliers/retailers, and user websites suggests that 4,4'-DMAR has been sold both as a drug in its own right and in tablet forms with a similar appearance to 'ecstasy' tablets. In the latter case, users may be unaware that they are using 4,4'-DMAR.

Route of administration, dose and drug regimens

Information provided by the Member States and from user websites suggests that the routes of administration for 4,4'-DMAR include nasal insufflation and oral (including consumption of tablets and 'bombing', the practice of wrapping powder in cigarette paper and swallowing) (chemsrus.com, 2014; drugs-forum.com, 2014; serotonin.info, 2014; ukchemicalresearch.org, 2014). In one of the death cases reported by Hungary, the route of administration of 4,4'-DMAR was by injection. The physical forms detected in seizures would appear to be consistent with these routes of administration.

Information from user websites, while limited, suggests that a range of 'doses' are used. 'Low doses' were reported as 10–15 mg insufflated or 10–25 mg oral with a 'high oral dose' being reported as 120 mg (drugs-forum.com, 2014). Another site reported the 'dosage' (not further described) as 30–100 mg (serotoni.info, 2014). Oral 'doses' between 60 and 200 mg and 65 mg insufflated have also been mentioned (ukchemicalresearch.org, 2014; chemsrus.com, 2014).

Information from user websites suggests that 4,4'-DMAR may be used on its own or in combination with other new psychoactive substances and/or controlled drugs (drugs-forum.com, 2014). In all of the 27 deaths reported by the Member States and in 12 of the 18 biological samples reported by Hungary related to the consumption of narcotics, one or more new psychoactive substances and/or controlled drugs (and/or their metabolites) were detected post-mortem (Annex 2).

Subjective effects

No studies were identified that have examined the subjective effects of 4,4'-DMAR in humans; information is limited to that

provided in a very small number of self-reported experiences from user websites. Onset is described as being fast, within 10 to 60 minutes, with effects lasting several hours (ukchemicalresearch.org, 2014; drugs-forum.com, 2014). Subjective effects appear to be those related to stimulant-type drugs. One user who reported having taken alcohol and an unspecified 'triple re-uptake inhibitor' prior to using 4,4'-DMAR noted increased heart rate, increased body temperature, jaw clenching, facial spasms, sweating, stimulation, psychosis and hallucinations (ukchemicalresearch.org, 2014). Another report described a similarity to the effects of MDMA, noting 'an extremely long stimulated comedown' (chemsrus.com, 2014). This is mirrored by a comment that 'the hallmark of this drug is its long half-life' (drugs-forum.com, 2014).

Availability, supply and price

EMCDDA monitoring in May 2014 of Internet retailers selling 4,4'-DMAR identified two retailers that were selling the substance. The first site marketed 4,4'-DMAR as a 'research chemical'. It was advertised in powder form only, with quantities ranging from 500 mg (EUR 18.10) to 100 g (EUR 220). All quantities above 500 mg appeared to be offered with large price discounts ranging from 55–80 %, depending on the quantity purchased. This retailer was the same site from which the collected sample of 4,4'-DMAR was obtained (reported by the United Kingdom, section 3.2.2). The second site offered 4,4'-DMAR in powder form; further details including the quantities available and price were only available on application to the site. Four retailers were identified that appear to have discontinued the sale of 4,4'-DMAR; the reasons for this were not provided.

Seizure data reported by the Member States suggest that 4,4'-DMAR is also sold directly on the illicit drug market as ecstasy; no information was reported on the price of 4,4'-DMAR when sold as ecstasy.

Prevalence of use

No prevalence surveys were identified that have examined the use of 4,4'-DMAR in the general population or in targeted populations. Information from seizures and deaths reported by the Member States suggests that in some cases 4,4'-DMAR is sold as ecstasy, although the extent of this practice is unknown.

3.5. Information on whether or not the new substance is currently under assessment, or has been under assessment, by the UN system — Article 5.2(e) of the Council Decision

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 para-methyl-4-methylaminorex (i.e. 4,4'-DMAR) is currently not under assessment and has not been under assessment by the United Nations system.

3.6. The date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol — Article 5.2(f) of the Council Decision

The first official notification to the EMCDDA of 4,4'-DMAR dates from 10 December 2012 from the Netherlands national focal point. The Reporting Form details a seizure of 500 g of white powder on 19 November 2012 by customs authorities at Amsterdam. The importation was noted to have arrived from India. The identification was based on the analytical techniques of NMR ⁽⁶⁾ and GC-MS ⁽⁷⁾, and it was also noted that this substance partly decomposes under certain conditions when using GC-MS.

4,4'-DMAR was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through the Early Warning System and a profile of the substance was created in the EMCDDA European Database on New Drugs (EDND). Since then analytical details, background information and public health alerts have been exchanged between EMCDDA, Europol and the Member States on an ad hoc basis. The Commission and the EMA were kept duly informed.

3.7. Information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State — Article 5.2(g) of the Council Decision

Hungary reported that 4,4'-DMAR is subject to control measures under drug control legislation. It 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).

In Poland, 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 and as such its marketing and production is penalised with a fine.

⁽⁶⁾ Nuclear magnetic resonance spectroscopy.

⁽⁷⁾ Gas chromatography-mass spectroscopy.

Finland and Norway reported that 4,4'-DMAR is subject to control measures under medicines legislation. In Finland it has been controlled since 12 March 2014 under the Medicines Act (395/87).

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'.

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

3.8. Further information — Article 5.2(h) of the Council Decision

3.8.1. The chemical precursors that are known to have been used for the manufacture of the substance

No information was reported by the Member States, Turkey or Norway about the chemical precursors or manufacturing methods used to make the 4,4'-DMAR that has been detected on the drug market.

Methods for the production of 4,4'-DMAR are documented in the literature. One such method describes the production of 4,4'-DMAR in five reaction steps using 4'-methylpropiophenone as the precursor. 4'-methylpropiophenone appears to be readily available from chemical suppliers. The 4'-methylpropiophenone precursor is first α -brominated, then the resulting alpha-bromo ketone intermediate is reacted with sodium diformylamide to give the *N,N*-diformamide derivative. Hydrolysis of this under acidic conditions provides access to the primary amine intermediate 4-methylcathinone which, following its reduction to 4-methylnorephedrine, can be converted to either (\pm)-*cis*-4,4'-DMAR via cyanogen bromide or (\pm)-*trans*-4,4'-DMAR via potassium cyanate. In addition, it is noted that the synthesis of 4,4'-DMAR shares a number of steps that are also employed for the synthesis of cathinone derivatives (Brandt et al., 2014).

3.8.2. The mode and scope of the established or expected use of the new substance

No studies were identified that have examined the mode and scope of established or expected use of 4,4'-DMAR. Given the limited information currently available, the relevant information reported by the Member States has been included in the previous sections. It is important to note in this respect that information from seizures and deaths suggest that 4,4'-DMAR may be sold as ecstasy directly on the illicit drug market.

Settings of use

No studies were identified that have examined the settings of use of 4,4'-DMAR. Information from the deaths reported by the Member States suggests that 4,4'-DMAR may be used in a range of settings (Annex 2).

3.8.3. Other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks

No information was provided by the Member States, Turkey or Norway that indicated that 4,4'-DMAR had any other use apart from in analytical reference materials and in legitimate scientific research into its chemistry, pharmacology and toxicology as a result of its emergence on the drug market.

From the available information it does not appear that 4,4'-DMAR is used in the manufacture of a medicinal product in the European Union. However, the collection of information cannot be considered exhaustive in the absence of a European Union database on the synthetic routes of all medicinal products ⁽⁸⁾.

4. Information from the EMA as requested by Article 5.3 of the Council Decision

4.1. Marketing authorisation

Twenty-one Member States, Iceland and Norway responded to the EMA's information request (section 2). They reported that the new psychoactive substance 4,4'-DMAR has not obtained

⁽⁸⁾ I.e. products that have been granted a marketing authorisation, or where an application for a marketing authorisation has been made, or where the marketing authorisation has been suspended.

a marketing authorisation ⁽⁹⁾. The EMA also reported that the new psychoactive substance 4,4'-DMAR has not obtained a marketing authorisation through the central authorisation procedure.

4.2. Application for a marketing authorisation

Twenty-one Member States, Iceland and Norway responded to the EMA's information request (section 2). They reported that the new psychoactive substance 4,4'-DMAR is not the subject of an application for a marketing authorisation ⁽⁹⁾. The EMA also reported that the new psychoactive substance 4,4'-DMAR is not the subject of an application for a marketing authorisation through the central authorisation procedure.

4.3. Suspended marketing authorisation

Twenty-one Member States, Iceland and Norway responded to the EMA's information request (section 2). They reported that there had been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance 4,4'-DMAR ⁽⁹⁾. The EMA also reported that the new psychoactive substance 4,4'-DMAR is not the subject of a suspended marketing authorisation through the central authorisation procedure.

5. Conclusion

4,4'-DMAR is a di-substituted 2-amino-5-phenyl oxazoline substance that appears to have stimulant properties. It is a derivative of aminorex and 4-methylaminorex, both synthetic stimulants that are controlled under the 1971 United Nations Convention on Psychotropic Substances.

An *in vitro* study has shown that (±)-*cis*-4,4'-DMAR is a potent, efficacious substrate-type releaser at transporters for dopamine, norepinephrine and serotonin.

4,4'-DMAR has been available on the European Union drug market since at least November 2012 and has been detected in seven Member States. One Member State has reported large powder seizures (>260 kg) by its customs authorities. It has been detected in tablets, some of which have markings resembling ecstasy tablets' markings, and in powder form. It appears that its availability from Internet retailers has decreased in recent months.

One Member State has reported the production of tablets, and that organised crime groups are involved in the trafficking and distribution of 4,4'-DMAR. A precursor that may be used for the production of 4,4'-DMAR appears to be readily available from chemical suppliers.

Twenty-seven deaths have been reported in two Member States with analytical confirmation of 4,4'-DMAR in post mortem samples; at least one other substance was present in each of these cases. On this basis, the potential impact from the further spread of 4,4'-DMAR on public health is a key concern.





We conclude that the health and social risks caused by the manufacture, trafficking and use of 4,4'-DMAR, and the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure in accordance with Article 6 of Council Decision 2005/387/JHA.

⁽⁹⁾ Austria, the Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Iceland, Ireland, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom provided responses in relation to both human and veterinary medicinal products. Italy and Lithuania provided responses in relation to human medicinal products. Belgium, France, Latvia and Poland provided responses in relation to veterinary medicinal products. In addition, the EMA provided information in relation to both human and veterinary medicinal products in respect of the central authorisation procedure.

References

- | Brandt, S. D., Baumann, M. H., Partilla, J. S., Kavanagh, P. V., Power, J. D., Talbot, B., et al. (2014), 'Characterization of a novel and potentially lethal designer drug, (±)-*cis-para*-methyl-4-methylaminorex (4,4'-DMAR, or 'Serotoni')', *Drug Testing and Analysis*, 19 May 2014.
- | Chemsrus.com (2014), www.chemsrus.com/forum/6-stimulants/7358-serotoni?limit=10&start=40. Accessed April 2014.
- | Davis, F. T. and Brewster, M. E. (1988), 'A fatality involving U4Euh, a cyclic derivative of phenylpropanolamine', *Journal of Forensic Sciences* 33, p. 549.
- | Drugs-forum.com (2014), www.drugs-forum.com/forum/showthread.php?t=216908#ixzz30NgkF9kJ. Accessed April 2014.
- | Klein, R. F. X., Sperling, A. R., Cooper, D. A. and Kram, T. C. (1989), 'The stereoisomers of 4-methylaminorex', *Journal of Forensic Sciences* 34, p. 962.
- | Serotonin.info (2014), www.serotoni.info. Accessed April 2014.
- | Ukchemicalresearch.org (2014), www.ukchemicalresearch.org/Thread-Serotoni-Powder-Serotonin-Syndrome-and-Stimulant-Psychosis. Accessed April 2014.

Annex 1**Images of 4,4'-DMAR from seizures and collected samples**

Country	Image	Description
Hungary		Seizures: 2013
Sweden		Seizure: 6 December 2013 Tablets, seized in Stockholm Seizing authority: customs
United Kingdom		Seizures: between June and August 2013 Tablets, seized in Northern Ireland Seizing authority: police
		Collected sample: March 2014 White powder Collecting authority: School of Pharmacy and Biomolecular Sciences (Liverpool John Moores University) and ROAR Forensics (Malvern).

Annex 2

Deaths associated with 4,4'-DMAR reported by Hungary and the United Kingdom

Case	MS	Date of death	Age	Sex	Matrix	4,4'-DMAR concentration	Other substances detected and concentration (where available)	Adverse events/autopsy findings	Additional information reported
1	HU	Jun 2013	25	M	Blood ^f	1.158 mg/L	7-Amino-clonazepam 0.1405 mg/L alpha-PVP 0.0056 mg/L Pentredone 0.0274 mg/L	High body temperature, extensive bleeding in the muscles.	No information on route of administration, however 'there was no pin-prick'.
					Urine	43.493 mg/L	7-Amino-clonazepam 0.0961 mg/L alpha-PVP 0.0908 mg/L Clonazepam 0.0137 mg/L 4-MEC 6.522 mg/L Pentredone 15.276 mg/L		
2	HU	Jun 2013	25	F	Blood ^f	0.0427 mg/L	Amphetamine 0.4918 mg/L alpha-PVP 0.2357 mg/L Midazolam 0.2374 mg/L	High body temperature, extensive bleeding in the muscles and organs. Confusion, disorientation, unconsciousness, perspiration.	Injected, use about 3 pm, 12 hours later died in the hospital.
3	HU	Jun 2013	18	M	Blood ^u	+ (no quantitation)	Mephedrone (no quantitation) MDMA (no quantitation) Pentredone (no quantitation)	Myoclonus, unconsciousness, body temperature: 42.9°C, internal bleeding (oral, intestinal), cardiac and respiratory arrest. Autopsy: large brain oedema, diffuse internal bleeding, bleeding in lungs, dilatation of the right ventricle and atrium.	Went out, did not go home. His parents found him on the street, in poor condition. Ambulance took him to the hospital, next morning died.
4	HU	Aug 2013	43	F	Blood ^f	2.055 mg/L	Mephedrone 0.5723 mg/L alpha-PVP 0.014 mg/L Alprazolam 0.1124 mg/L	—	She was found at home. She had died 2–3 days before. No information on route of administration; however, 'there was no pin-prick'.
					Urine	5.928 mg/L	Mephedrone 0.3215 mg/L alpha-PVP 0.0056 mg/L Alprazolam 0.0534 mg/L OH-Alprazolam 0.027 mg/L		
5	HU	Sep 2013	20	F	Blood ^f	3.565 mg/L	Alprazolam 0.0951 mg/L alpha-PVP 0.0296 mg/L Pentredone 0.1730 mg/L THC-COOH 0.0127 mg/L	—	She died after a party. No information on route of administration; however, 'there was no pin-prick'.
					Urine	32.945 mg/L	Pentredone 44.544 mg/L Amphetamine 0.353 mg/L alpha-PVP 0.0844 mg/L Alprazolam 0.0167 mg/L		

Case	MS	Date of death	Age	Sex	Matrix	4,4'-DMAR concentration	Other substances detected and concentration (where available)	Adverse events/autopsy findings	Additional information reported
6	HU	Oct 2013	18	F	Blood ^u	+ (no quantitation)	MDA 0.0251 mg/L MDMA 0.1989 mg/L	Agitation, sweat, pale. 41.2°C temperature, glucose 1.7 mmol/l. Autopsy: brain oedema, bleeding and oedema in the lungs, 'shock' kidneys.	She consumed drugs with her friend in the afternoon. Parents took her to the hospital, after 1 hour she died (arrived: 23:05, died: 00:04).
7	HU	Oct 2013	27	M	Blood ^u Urine	+ (no quantitation) + (no quantitation)	MDA 0.04 mg/L MDMA 0.8863 mg/L Mephedrone 0.0363 mg/L MDA (no quantitation) MDMA (no quantitation) Mephedrone (no quantitation)	Mild brain oedema, shock, in the heart right atrial and ventricular dilatation, intestinal bleeding.	He consumed drugs with his friends at 18:30, died next morning.
8	HU	Oct 2013	37	M	Blood ^u	+ (concentration to be confirmed)	MDA (concentration to be confirmed) MDMA (concentration to be confirmed)	Autopsy: cardiomyopathy, brain edema, pulmonary edema, tonsillar herniation, emollient brain tissue.	—
9	UK	Jun 2013	36	M	Blood ^f	0.66 mg/L	Benzoyllecognine 0.97 mg/L Cocaine <0.05 mg/L Codeine <0.02 mg/L Tetra/levamisole (unconfirmed)	—	—
10	UK	Jun 2013	25	M	Blood ^f	0.9 mg/L	4-MEC 0.05 mg/L MDMA 0.82 mg/L MDA PMMA 0.11 mg/L PMA THC-COOH	—	Drinking heavily, took 'methadone', continued drinking, took 2 'ecstasy' tabs immediately felt unwell, agitated. Unresponsive 1 hr later.
11	UK	Jun 2013	33	M	Blood ^f	0.28 mg/L	Benzoyllecognine 0.04 mg/L	—	Believed to have taken 'cocaine and ecstasy'. Deceased had taken 'speckled cherries tablets' orally. Cerebral oedema at post mortem, suspected to have taken drugs at 14:30, found unconscious the following day at 07:30, died in hospital the day after at 10:30.
12	UK	Jun 2013	27	M	Blood ^f	0.7 mg/L	Benzoyllecognine 0.36 mg/L MDMA 0.19 mg/L MDA Mirtazapine (a low level) Indications of low level of cocaine	—	4,4'-DMAR detected on nasal swabs with cocaine. Found dead on arrival of ambulance service, tablets and powder found when house searched.

Case	MS	Date of death	Age	Sex	Matrix	4,4'-DMAR concentration	Other substances detected and concentration (where available)	Adverse events/autopsy findings	Additional information reported
13	UK	Jul 2013	29	M	Blood ^f	<0.02 mg/L	PMA 0.09 mg/L Diazepam plus metabolite 0.14 mg/L THC-COOH Indications of lidocaine	He appeared 'wiped out', was agitated and overheating, began foaming at mouth.	Friend purchased 10 x speckled cherries for £50, two weeks prior, from an unknown male in a bar. Socialising with friends at his flat drinking alcohol, taking 'E' 'speckled cherry', witness describes him taking 3 x 'speckled cherry' E tabs over the course of the evening.
14	UK	Jul 2013	40	M	Blood ^f	1.25 mg/L	MDMA 0.02 mg/L Diazepam 0.05 mg/L THC-COOH	—	Consumed alcohol, ecstasy and cannabis, found dead the next day, nothing at post mortem.
15	UK	Aug 2013	41	M	Blood ^f	3.13 mg/L	MDMA 0.3 mg/L MDA Citalopram 0.42 mg/L	Epileptic type seizure prior to death.	Deceased had taken 'speckled cherries tablets'. Alcoholic, heavy intake prior to death, epileptic type seizure prior to death, tablets at scene.
16	UK	Aug 2013	18	F	Blood ^f	2.1 mg/L	bk-MDMA 0.84 mg/L 4-MEC 0.72 mg/L FMC THC-COOH (low level)	—	Deceased had taken 'speckled cherries tablets'. Died at home following a house party (same location) after consuming an unknown quantity of ecstasy tablets and 'meth', tablets described as grey with cherry logo, witnesses speculate she consumed 2–3 tablets.
17	UK	Aug 2013	19	F	Blood ^f Blood ^u (ante mortem)	~0.85 mg/L 1.8 mg/L	4-MMC ~0.045 mg/L 4-MMC <0.01 mg/L 4-MEC <0.01 mg/L bk-MDMA <0.01 mg/L	—	Collapsed at a party, suspected overdose, taken to hospital unconscious and later died. Witnesses described her 'consuming ecstasy and snorting meth'.
18	UK	Aug 2013	20	M	Blood ^f	1.6 mg/L	4-MEC 1.68 mg/L bk-MDMA 0.26 mg/L 4-MMC (low level) Diazepam (low level) THC-COOH Indications FMC	Suffered seizure.	Deceased had taken 'speckled cross tablet'. Suffered seizure and died, unidentified tablets and 9.36 g of powder was seized at the scene. Powder contained 4-MEC, bk-MDMA, fmc? (no quantification). Unclear if this powder was linked to the deceased as more than one person was present in the house. 4,4'-DMAR and 4-MMC detected on nasal swabs taken post-mortem.

Case	MS	Date of death	Age	Sex	Matrix	4,4'-DMAR concentration	Other substances detected and concentration (where available)	Adverse events/autopsy findings	Additional information reported
19	UK	Sep 2013	21	M	Blood ^f	0.21 mg/L	4-MMC 0.02 mg/L 4-MEC 0.1 mg/L bk-MDMA 0.07 mg/L Diazepam 0.03 mg/L THC-COOH Amiodarone	Agitated state, sweating profusely, and had problems breathing.	Alcohol, one or two ecstasy tablets, speckled cherry possibly green, 'methadrone' had been consumed. Taken to hospital (arrived 18:57), after taking ill at a house party. Agitated state, sweating profusely, and had problems breathing, deteriorated rapidly, pronounced dead 23:10. Had been partying for the previous two/three days.
20	UK	Sep 2013	31	M	Blood ^f	1.72 mg/L	Benzoylcoognine 0.55 mg/L Indications of low levels of cocaine and desmethyldiazepam	Cardiac arrest.	Drinking and taking drugs (ecstasy and cocaine, 4 x 'blue') in his home with two friends in the morning, became unwell at 11.00, unresponsive when paramedics attended, taken to hospital, suffered cardiac arrest, and died at 12:24. Two witnesses also admitted to hospital, one said they had all taken drugs and deceased had taken 4 'blues' in one go.
21	UK	Nov 2013	21	M	Blood ^f	1.75 mg/L	bk-MDMA 0.14 mg/L 4-MEC 0.06 mg/L 4-MMC 0.04 mg/L THC-COOH	18.00: sweating, paranoid thoughts; midnight: sweating profusely, convulsion, cardiac arrest.	No previous history of drug abuse. Thought to have taken e tabs. Mirtazapine prescribed, atropine and adrenaline administered.
22	UK	Nov 2013	16	F	Blood ^f	1.1 mg/L	Indications of diazepam (low level) Lidocaine Amiodarone Methylprednisolone?	Cardiac arrest.	Cardiac arrest while out with friends. PMH asthma.
23	UK	Dec 2013	30	M	Blood ^f	<0.02 mg/L	Olanzapine 0.66 mg/L Diazepam plus metabolite 0.41 mg/L Codeine 0.13 mg/L Paracetamol 11.1 mg/L Indications of pregabalin	—	History of drug misuse, overdoses and mental illness.
24	UK	Dec 2013	33	M	Blood ^f	1.01 mg/L	4-MEC (low level) bk-MDMA 0.22 mg/L Diazepam plus metabolite (low level) THC-COOH	—	Thought to have taken 'plant food'.
25	UK	Dec 2013	—	—	Blood ^f	1.72 mg/L	THC-COOH BAC 53 mg% UAC 87 mg%	—	Found dead in bed, had been drinking heavily, history of drug abuse including ecstasy.

Case	MS	Date of death	Age	Sex	Matrix	4,4'-DMAR concentration	Other substances detected and concentration (where available)	Adverse events/autopsy findings	Additional information reported
26	UK	Dec 2013	41	M	Blood ^f	3.75 mg/L	4-MEC 0.53 mg/L MDMA 0.72 mg/L MDA THC-COOH Quetiapine (a low level)	Shaking all over, sweating, having a fit, hands stuck open with fingers squeezing together like claws.	Call to ambulance service reported a male taking ecstasy and going into cardiac arrest. At the time of his death he was hosting a party, a large quantity of drugs were allegedly available, 'cocaine, speckled Rolex ecstasy tablets, magic and cannabis' and alcohol. Severe heart disease at post mortem.
27	UK	Feb 2014	35	M	Blood ^f	3.5 mg/L	bk-MDMA 0.33 mg/L 4-MEC 0.16 mg/L FMC 0.11 mg/L Procyclidine 0.11 mg/L Diazepam 0.06 mg/L Desmethyldiazepam 0.09 mg/L THC-COOH	Fitting, unconscious and breathing.	Taking ecstasy tablets and legal highs, 'taking cocaine and ecstasy', 'fitting, unconscious and breathing' when ambulance called at approx. 03:13, police and ambulance arrived 03:21, deceased. Other person present taken to hospital described as critical.

Note: in all cases 4,4'-DMAR was analytically confirmed in post-mortem biological samples.

Key: MS: Member State; HU: Hungary; UK: United Kingdom; M: male; F: female; Blood^f: femoral blood sample; Blood^u: site of blood sample unspecified; -: Not reported.

Recommended citation:

European Monitoring Centre for Drugs and Drug Addiction (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.

About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

The EMCDDA's publications are a prime source of information for a wide range of audiences including: policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

Related publications and websites**EMCDDA**

| *European Drug Report 2014: Trends and developments*, 2014

EMCDDA and Europol

| *EMCDDA–Europol 2013 Annual Report on the implementation of Council Decision 2005/387/JHA*, Implementation reports, 2014

These and all other EMCDDA publications are available from www.emcdda.europa.eu/publications

| EMCDDA Action on new drugs: www.emcdda.europa.eu/drug-situation/new-drugs

Legal notice: The contents of this publication do not necessarily reflect the official opinions of the EMCDDA's partners, the EU Member States or any institution or agency of the European Union. More information on the European Union is available on the Internet (europa.eu).

Luxembourg: Publications Office of the European Union
doi: 10.2810/51897 | ISBN 978-92-9168-743-5

© European Monitoring Centre for Drugs and Drug Addiction, 2014
Reproduction is authorised provided the source is acknowledged.

This publication is only available in electronic format.

EMCDDA, Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal
Tel. (351) 211 21 02 00 | info@emcdda.europa.eu
emcdda.europa.eu | twitter.com/emcdda | facebook.com/emcdda