ANNEX 1

Technical report on 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-dimethylaminorex, 4,4'-DMAR)

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Summary

The substance 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-dimethylaminorex, 4,4'-DMAR) is a synthetic, substituted oxazoline derivative. 4,4'-DMAR is also a derivative of 4-methylaminorex (4-MAR) and aminorex, both of which are stimulants and controlled under the 1971 United Nations Convention on Psychotropic Substances. Limited information suggests that 4,4'-DMAR has stimulant-type effects.

The detection of 4,4'-DMAR on the European drug market was first officially notified to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) through the EU Early Warning System by the Netherlands national focal point on 10 December 2012 and related to a seizure made by customs authorities of 500 g of white powder that had arrived from India in the previous month. Nine Member States (Denmark, Finland, France, Hungary, the Netherlands, Poland, Romania, Sweden and the United Kingdom) reported detections ([1]) of 4,4'-DMAR. This substance has typically been seized as powders or tablets. In most cases, 4,4'-DMAR was reported as the only active constituent, while in about 20 % of detections it was found in combination with other substances. Most of the Member States reported a small number of seizures; however, in the case of the Netherlands these totalled more than 90 kg of powder.

Chemically, 4,4'-DMAR can exist in the form of two different racemic (±)-*cis* and (±)-*trans* mixtures or four distinct enantiomers. In cases where sufficient analytical data were available from collected and biological sample analyses, the presence of the *cis* form was indicated. Whether the *trans* isomers are also available on the drug market is currently not known.

4,4'-DMAR has been advertised under the name 'Serotoni' and is available for purchase from online retailers as a 'research chemical' in either powder or tablet/pellet form. It appears that the number of Internet shops advertising this particular substance may be declining. Information from the Member States suggests that 4,4'-DMAR is sold as a drug in its own right, and surreptitiously as ecstasy and other illicit drugs. Seized tablets found to contain 4,4'-DMAR showed a range of shapes, markings and logos ([2]), thus raising the likelihood that these particular products were designed to be sold as 'ecstasy' tablets on the illicit drug market.

One analytically confirmed non-fatal intoxication has been reported by Poland and 31 deaths associated with 4,4'-DMAR have been reported by Hungary (eight deaths), Poland (one death) and the United Kingdom (22 deaths). The deaths in Hungary occurred between June and October 2013, the Polish death occurred in July 2013 and those in the United Kingdom occurred between June 2013 and June 2014. Data on gender and age are currently available for 30 of the decedents. Twenty-two were male (four from Hungary; one from Poland; 17 from the United Kingdom); eight were female (four from Hungary; four 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 31 deaths. With the exception of one case, the presence of one or more psychoactive substances (and/or their metabolites) in post-mortem biological samples was noted.

There are no coordinated national or European population surveys on the prevalence of 4,4'-DMAR use. There is no information to suggest that 4,4'-DMAR has any industrial, cosmetic or medicinal use.

([1]) '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 from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).

([2]) 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.

Compared to other types of new psychoactive substances (such as the synthetic cathinones) there are limited self-reported experiences with 4,4'-DMAR on user websites. 4,4'-DMAR appears to be generally recognised by users as a stimulant, and is used in a range of 'doses'. Single dosage levels may range between 10 mg and 200 mg, depending on the route of administration. Oral administration and nasal insufflation are commonly reported; inhalation of the drug has also been mentioned. In one of the deaths reported to the EU Early Warning System the drug had been injected (the specific route of injection was not reported). Warning messages have been posted on user websites by users about comparatively long-lasting effects and the potential for adverse reactions (such as perceived serotonin toxicity), especially when taken in combination with other substances including alcohol.

The first formal scientific investigations into the chemical, analytical and pharmacological properties of *cis*- and *trans*-4,4'-DMAR appeared in 2014. Monoamine transporter activity studies in rat brain synaptosomes using *d*-amphetamine, aminorex and 4-methylaminorex as control compounds, showed that *cis*-4,4'-DMAR was a potent, non-selective and fully efficacious substrate-type releaser at transporters for dopamine (DAT), norepinephrine (NET), and serotonin (SERT). The potency of *cis*-4,4'-DMAR at DAT and NET rivalled that of other psychomotor stimulant drugs like *d*-amphetamine and aminorex. However, *cis*-4,4'-DMAR had much more potent actions at SERT. The *trans*-4,4'-DMAR isomer was also found to be a potent releasing agent at DAT and NET while acting as an uptake blocker at SERT, thus showing a 'hybrid' profile. Both *cis*- and *trans*-4,4'-DMAR isomers were also more potent than (*S*)-(+)-3,4-methylenedioxymethamphetamine ((*S*)-(+)-MDMA) as catecholamine releasers.

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical and pharmaceutical information

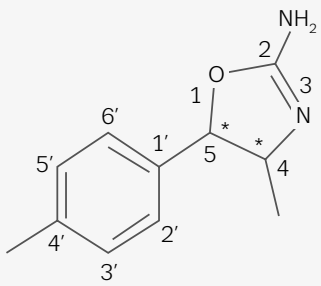
A1.1. Physical and chemical description

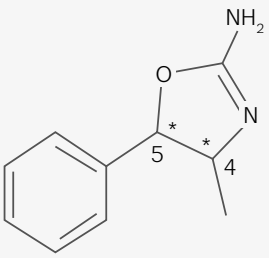
Chemical description and names

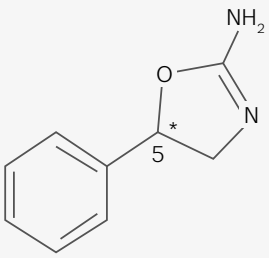
4-Methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-DMAR) is a synthetic substituted oxazoline derivative. It can also be classified as an analogue of 4-methylaminorex (4-MAR) and aminorex, both of which are psychostimulants and controlled under the 1971 United Nations Convention on Psychotropic Substances ([3]). The structures of 4,4'-DMAR, 4-MAR and aminorex are provided in Figure 1.

FIGURE 1

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







4,4'-DMAR	4-MAR	Aminorex
Molecular formula: $C_{11}H_{14}N_2O$	Molecular formula: $C_{10}H_{12}N_2O$	Molecular formula: $C_9H_{10}N_2O$
Molecular weight: 190.25	Molecular weight: 176.22	Molecular weight: 162.19
Monoisotopic mass: 190.1106	Monoisotopic mass: 176.0950	Monoisotopic mass: 162.0793

Note: Structures of 4-MAR and aminorex are provided for comparison. Asterisk indicates chiral carbon.

([3]) 4-MAR is listed in Schedule I and aminorex is listed in Schedule IV of the 1971 United Nations Convention on Psychotropic Substances.

TABLE 1

Alternative names, codenames, street names, and abbreviations that may be encountered for 4,4'-DMAR

4-Methyl-5-(*p*-tolyl)-4,5-dihydrooxazol-2-amine
4,5-Dihydro-4-methyl-5-(4-methylphenyl)-2-oxazolamine
[4-Methyl-5-(*p*-tolyl)-2-oxazolin-2-yl]amine
4-Methyl-5-(*para*-methylphenyl)-2-amino-oxazoline
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
ST60

The systematic (International Union of Pure and Applied Chemistry, IUPAC) name is 4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine. Other commonly encountered names, codenames, street names, and abbreviations are given in Table 1. Chemical Abstract Service (CAS) registry numbers are given in Table 2.

TABLE 2

Chemical Abstract Service (CAS) Registry Numbers for 4,4'-DMAR

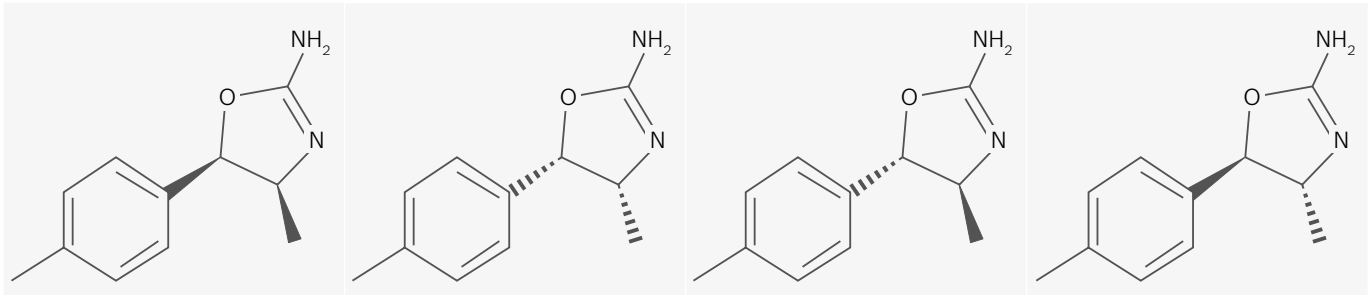
CAS Registry Numbers	Variant
1445569-01-6	Form not specified
364064-08-4	(4S,5S) Free base

The words 'euphoria' and 'U4Euh', used in some of the street names of 4,4'-DMAR (Table 1), are references to two of the street names given to 4-methylaminorex (4-MAR) ([4]), a psychostimulant encountered in the 1980s (By et al., 1989; Cooper, 1988; Davis and Brewster, 1988; Klein et al., 1989). Aminorex ([5]), i.e. the analogue without both methyl groups at the *para*- and 4-position contained in 4,4'-DMAR, was briefly available as an appetite suppressant in Europe during the late 1960s but was withdrawn from the market due to an association with primary pulmonary hypertension (Gurtner, 1979, 1985).

The presence of two chiral centres within the oxazoline ring of 4,4'-DMAR gives rise to four enantiomers or two (±)-*cis* and (±)-*trans* racemates, as shown in Figure 2 ([6]). However, it seems unlikely that any of the enantiopure forms would appear on the drug market, due to additional complexities involved in their preparation.

FIGURE 2

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



(4*S*,5*R*)-4,4'-DMAR	(4*R*,5*S*)-4,4'-DMAR	(4*S*,5*S*)-4,4'-DMAR	(4*R*,5*R*)-4,4'-DMAR
Racemic form: (±)-*cis*-4,4'-DMAR or (4/SR/,5/RS/)-4,4'-DMAR		Racemic form: (±)-*trans*-4,4'-DMAR or (4/SR/,5/SR/)-4,4'-DMAR	

([4]) Other street names for 4-methylaminorex include: 4-MAX, McN-822 and 'ICE' (before this term was more frequently used for methamphetamine).

([5]) 5-Phenyl-4,5-dihydro-1,3-oxazol-2-amine (aminoxafen; aminoxaphen; apiquel; CPDD-0039; McN-742; NSC-66592; NSC-66952).

([6]) (±) is used to denote the presence of the racemic mixture. For reasons of clarity it will be omitted in the remaining text when reference is made to either *cis*- or *trans* 4,4'-DMAR instead of (±)-*cis*- and (±)-*trans*-4,4'-DMAR, respectively.

Identification and analytical profile

An extensive analytical characterisation and preparation of both *cis*- and *trans*-4,4'-DMAR racemates has recently been reported (Brandt et al., 2014). These included ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR), electron- and chemical ionisation (EI/CI), electrospray (ESI) triple quadrupole and high-resolution mass spectrometry, Fourier transform infrared spectroscopy (FTIR), ultraviolet-visible spectroscopy, gas (GC)- and liquid chromatography (LC) and X-ray crystallography. The differentiation of *cis* and *trans* racemates may be facilitated by implementation of FTIR, NMR or adequate separation techniques. Chiral resolution of all four enantiomers may be obtained from derivatisation and synthesis or separation using appropriate preparatory stationary phases.

Analysis by EI-MS revealed the presence of key fragments at *m/z* 190 ($M^{\bullet+}$), 175, 146, 119, 91, 70 (base peak) and m/z 43, respectively. The EI spectra of both racemates are identical as expected. Collision-induced dissociation of the protonated molecule $[M+H]^+$ at *m/z* 191 under ESI-MS/MS conditions gave key product ions at *m/z* 148 (base peak, depending on collision energy), 131, 116, 105, 91 and 56. Challenges (e.g. peak broadening or artificially induced isomerisation) may be encountered during characterisation by GC-MS. Differentiation between *cis*- and *trans*-4,4'-DMAR may also be obtained by NMR analysis:

cis-4,4'-DMAR free base: ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 7.8 Hz, 2 H, Ar H), 7.12 (d, J = 7.8 Hz, 2 H, Ar H), 5.74 (d, J = 8.7 Hz, H-5), 4.41 (dq, J = 8.7, 6.8 Hz, H-4), 2.38 (s, 3 H, Ar-CH_3) and 0.84 (d, J = 6.8 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 160.90 (C-2), 138.30 (Ar-C), 131.71 (Ar-C), 129.04 (Ar-CH), 125.85 (Ar-CH), 85.59 (C-5), 59.50 (C-4), 21.07 (Ar-CH_3) and 17.59 (CH_3).

trans-4,4'-DMAR free base: ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 4 H, Ar H), 5.08 (d, *J* = 7.7 Hz, 1 H, H-5), 4.05 (dq, J = 7.7, 6.2 Hz, 1 H, H-4), 2.38 (s, 3 H, Ar-CH_3) and 1.40 (d, *J* = 6.2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 160.49 (C-2), 139.34 (Ar-C), 133.84 (Ar-C), 129.76 (Ar-CH), 126.31 (Ar-CH), 90.25 (C-5), 63.71 (C-4), 21.03 (Ar-CH_3) and 20.08 (CH_3).

The direct analysis of 4,4'-DMAR (e.g. as a powder, tablet or in liquid form) can be carried out using standard techniques. Detection in biological fluids may require the implementation of more sensitive technology including single or tandem mass-spectrometry, in cases where low concentrations may be encountered in the sample matrices. Detection methods such as GC-MS, HPLC and/or LC-MS have been applied and published as part of a recent case series relating to 18 deaths associated with 4,4'-DMAR in the United Kingdom (Cosbey et al., 2014) ([7]) (Section D1.2.3). Data from these deaths and others reported by the United Kingdom, and data from a collected sample purchased from an Internet retailer ([8]), indicate that it is the *cis* form of 4,4'-DMAR on the drug market (Brandt et al., 2014). Information about the presence and prevalence of its *trans* counterpart is unavailable but the potential for its appearance cannot be excluded. The implementation of analytical procedures applied to low concentration sample matrices able to differentiate between the *cis* and the *trans* forms requires access to suitable reference material. It is worth noting that the preparation and analytical characterisation of the 3,4-dimethylaminorex isomers (both methyl groups present on the oxazoline ring) has been described in the literature (Noggle et al., 1992) and analytical differentiation from 4,4'-DMAR would not be expected to cause difficulties ([9]). One of the *trans* enantiomers appears to have been discussed on an online forum and called '4-DMAR' and 'Direx' ([10]).

There is no information on presumptive colour tests with 4,4'-DMAR.

As of August 2014 there is no immunoassay field test for 4,4'-DMAR. Data on cross-reactivity with commercially available urine immunoassay tests used for standard drugs of abuse are currently unavailable. Information related to a death reported by Poland (Section D1.2.3) noted that preliminary screening with an ELISA test pointed towards the presence of amphetamine, methamphetamine and benzodiazepines. Blood analysis carried out by LC-MS/MS, however, confirmed the presence of 4,4'-DMAR, *N*-ethylbuphedrone (NEB), midazolam and α-hydroxy-midazolam instead.

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS Registry Numbers listed above and no information was found.

Physical description

The free base of both *cis* and *trans* forms have been described as colourless solids with melting points of 136–138°C (*cis*-4,4'-DMAR) and 101–103°C (*trans*-4,4'-DMAR). The melting point of a recrystallised *cis*-4,4'-DMAR hydrochloride

([7]) These 18 deaths are included in those that have been reported by the United Kingdom.

([8]) The term 'Internet retailer' is used in this report to describe Internet shops that offer new psychoactive substances for sale, often advertising them as 'legal highs' and 'research chemicals'.

([9]) Another isomer 3',4-DMAR ('Serotoni 2.0'), i.e. carrying the methyl group in the meta- instead of the para-position, has been mentioned on the Internet (serotoni.info, 2014), although data on this compound seem to be unavailable at present.

([10]) www.drugs-forum.com/forum/showthread.php?t=83865 (August 2014).

salt sample obtained from an Internet retailer was given as 163–165°C (ethyl acetate/methanol) (Brandt et al., 2014) (Section C). The *cis*-4,4'-DMAR HCl salt is a white crystalline powder and soluble in water. Commercially available analytical reference standards for all enantiomers and both racemic forms are expected to be available in the near future. Section A1.2 provides a description of the physical forms reported by Member States.

Methods and chemical precursors used for the manufacture of 4,4'-DMAR

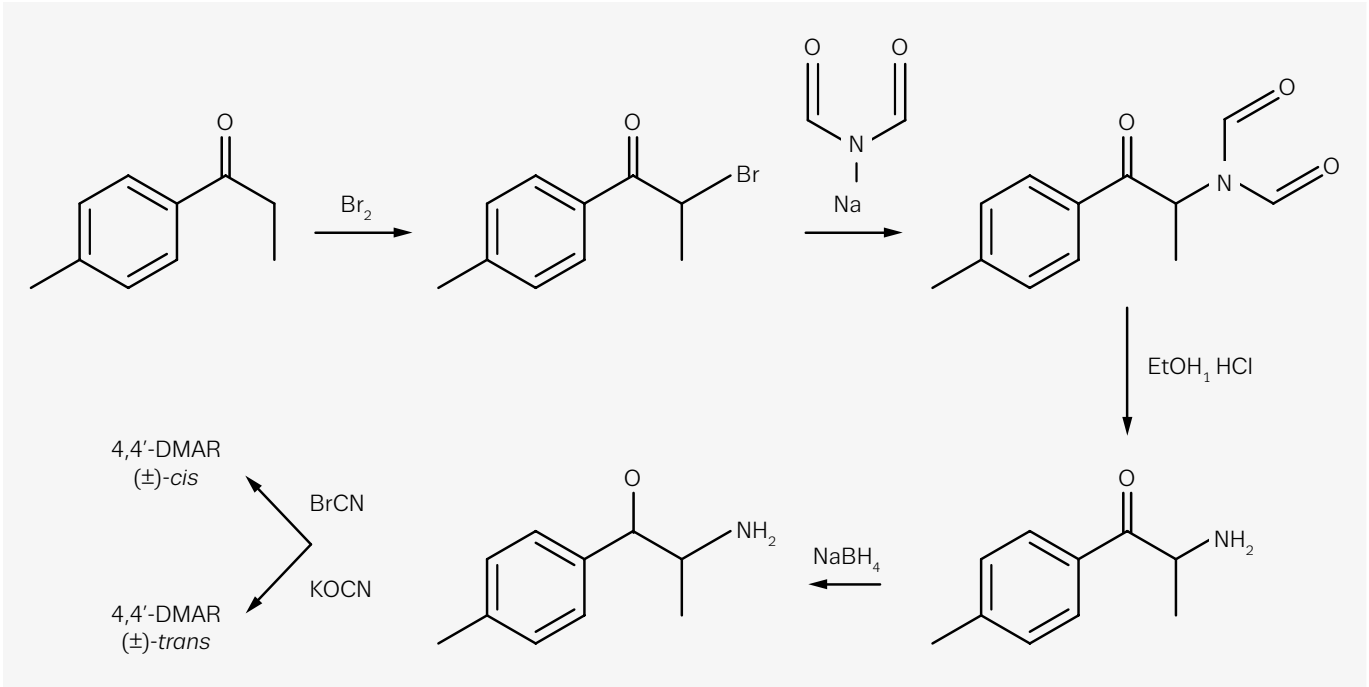
Information is not available regarding manufacturing sites, precursors or synthetic methods used for 4,4'-DMAR detected on the drug market in Europe. A report on the syntheses of *cis*- and *trans*-4,4'-DMAR was first published in 2014 and is outlined in Figure 3 (Brandt et al., 2014). Important key intermediates in this reaction are the cathinone (normephedrone) intermediate and the reduced alcohol. Conversion to *cis*- and *trans*-4,4'-DMAR was achieved with either cyanogen bromide (BrCN) or potassium cyanate (KOCN), respectively, based on a number of variations published in the earlier literature related to the chemistry of aminorex-type compounds (e.g. Fodor and Koczka, 1952; Poos et al., 1963; Rodriguez and Allred, 2005). Interestingly, the idea of synthesising 4,4'-DMAR following established aminorex-type chemistry was discussed on an online forum at least as early as 2003, although it is unclear whether this was ever taken further to the preparatory stage ([11]).

Typical impurities encountered in seized and collected samples

Detailed information is not available with regard to route-specific by-products produced during the synthesis of 4,4'-DMAR. In addition, there are no quantitative data currently available on the impurities detected in seized and collected samples. Analyses of seized powder and tablet materials (Section C) have revealed mixtures with other new psychoactive substances such as pentedrone ([12]), methcathinone, MPPP ([13]), alpha-PVP ([14]), bk-MPA ([15]),

FIGURE 3

Synthesis of *cis*- and *trans*-4,4'-DMAR, as reported by Brandt et al., 2014



([11]) For example, some of the files for 'The Hive' forum (defunct since 2004) have been archived ('Hive filez'). The contemplation on a potential 4,4'-DMAR synthesis was posted on 05.04.2003 (post no. 424141). The Hive was an online discussion forum for individuals interested in the practical synthesis of psychoactive substances, their use, and the related social and policy issues.
([12]) 2-(Methylamino)-1-phenylpentan-1-one
([13]) 1-(4-Methylphenyl)-2-(pyrrolidin-1-yl)propan-1-one
([14]) 1-Phenyl-2-(pyrrolidin-1-yl)pentan-1-one
([15]) 2-(Methylamino)-1-(thiophen-2-yl)propan-1-one

PVP ([16]), mephedrone ([17]), UR-144 ([18]), RH-34 ([19]), ethylphenidate and 5-APDB ([20]). In one case from Hungary, the presence of creatine monohydrate was reported to be present as a cutting agent. In the majority of cases 4,4'-DMAR was the main constituent.

A1.2. Physical/pharmaceutical form

Reports of seizures and collected samples have noted that 4,4'-DMAR has typically been obtained in the form of powders and tablets (EMCDDA and Europol, 2014). The majority of powders are white, but other samples have also been described as pale yellow, pink, green and blue coloured powders. Tablets have been observed in various colours and shapes, some of which bore logos such as 'Playboy', 'Heart', 'Mitsubishi', 'Star', 'Transformers', 'Cherries' and 'Cross'. The analysis of a collected sample of 5 g of 4,4'-DMAR in the form of a white powder sample obtained from an Internet retailer confirmed the presence of the *cis* form as a hydrochloride salt (Brandt et al., 2014). Section C provides further details of the seized and the collected sample of 4,4'-DMAR.

A1.3. Route of administration and dosage

Information provided by the Member States and from user websites ([21]) suggests that common routes of administration for 4,4'-DMAR are nasal insufflation and oral administration ([22]). In the latter case, consumption of tablets and 'bombing', i.e. the practice of wrapping powder in cigarette paper (or similar) prior to swallowing, have been noted. One self-reported experience from a user website notes the inhalation of 20 mg 4,4'-DMAR, which appeared to be based on the application of heat to what was described as a 'methpipe'. In this instance this was preceded by oral administration of 40 mg ([23]). In one of the deaths reported by Hungary to the EU Early Warning System the drug had been injected (specific route of injection not reported). The physical forms detected in seizures and the collected sample would appear to be consistent with these routes of administration (Section C).

Limited information on user websites 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 ([24]). Another site reported the 'dosage' (not further described) as 30–100 mg ([25]). Oral 'doses' of between 60 and 200 mg and 65 mg insufflation have also been mentioned, in addition to dosage levels of 'around 360 mg over the course of around 4–5 hrs' ([26]).

Information from Member States, particularly in relation to the deaths associated with 4,4'DMAR, and from user websites ([27]) suggests that 4,4'-DMAR may be used on its own or in combination with other psychoactive substances.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacodynamics

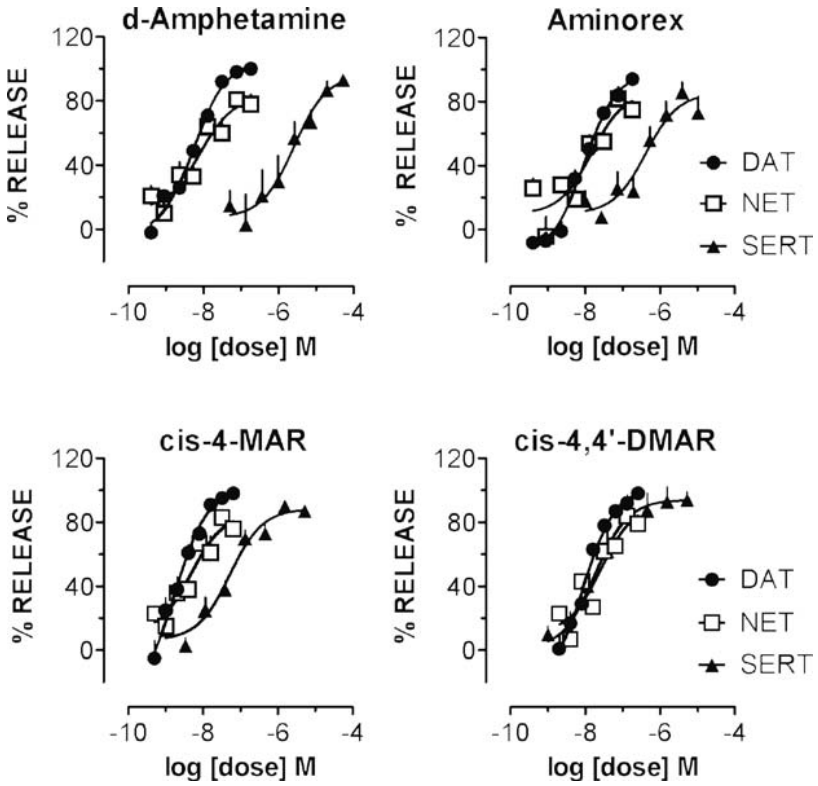
While a number of nonclinical studies have been published on the psychostimulant-like properties of 4-methylminorex (e.g. Ashby et al., 1995; Batsche et al., 1994; Bunker et al., 1990; Glennon and Misenheimer, 1990; Goodman, 1990; Hanson et al., 1992; Hanson et al., 1999; Kankaanpää et al., 2002; Mansbach et al., 1990; Meririnne et al., 2005; Roszkowski and Kelley, 1963; Russell et al., 1995; Yelnosky and Katz, 1963; Young and Glennon, 1993, 1998), data on 4,4'-DMAR are more limited due to its recent emergence on the drug market.

Recent *in vitro* investigations on the monoamine transporter activity of *cis*-4,4'-DMAR using rat brain synaptosomes (Baumann et al., 2012, Rothman et al., 2003) revealed a robust ability to induce release of dopamine, noradrenaline and serotonin at the dopamine transporter (DAT), noradrenaline transporter (NET) and serotonin transporter (SERT), respectively (Brandt et al., 2014). *d*-Amphetamine, aminorex and *cis*-4-MAR (4-methylaminorex) were used as control compounds. The determination of dose-response curves (Figure 4) and potency values (expressed as half maximal effective concentrations, EC_{50}, Table 3) revealed potent releasing activity of all compounds at DAT. Considerable potency values were also obtained for NET while activity at SERT varied more than 100-fold across the four substances, with (±)-*cis*-4,4'-DMAR exhibiting the highest potency at releasing serotonin (EC_{50} = 18.5 ± 2.8 nM). These results suggested that *cis*-4,4'-DMAR is a potent efficacious releaser at DAT, NET and SERT in rat brain tissue with comparable potency at DAT and NET to that of

([16]) Presumed to refer to alpha-PVP, i.e. 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one
([17]) 2-(Methylamino)-1-(4-methylphenyl)propan-1-one
([18]) (1-Pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
([19]) 3-{2-[(2-Methoxybenzyl)amino]ethyl}quinazoline-2,4(1H,3H)-dione
([20]) 1-(2,3-Dihydro-1-benzofuran-5-yl)propan-2-amine
([21]) The term 'user website' is used to describe Internet drug discussion forums and related websites.
([22]) www.chemsrus.com (2014); www.drugs-forum.com (2014); serotoni.info (2014); www.bluelight.org (2014); www.ukchemicalresearch.org (2014).
([23]) www.zoklet.net/bbs/showthread.php?t=289735 (15 August 2014).
([24]) www.drugs-forum.com/forum/showthread.php?t=216908 (April 2014).
([25]) serotoni.info (April 2014).
([26]) www.ukchemicalresearch.org/Thread-Serotoni-Powder-Serotonin-Syndrome-and-Stimulant-Psychosis (April 2014) and www.chemsrus.com/forum/6-stimulants/7358-serotoni?limit=10&start=40 (April 2014).
([27]) www.drugs-forum.com/forum/showthread.php?t=216908 (April 2014).

FIGURE 4

Dose-response effects of *d*-amphetamine, aminorex, *cis*-4-MAR and *cis*-4,4'-DMAR in evoking release from DAT, NET and SERT in rat brain synaptosomes (Brandt et al., 2014)



d-amphetamine and aminorex. Table 3 also shows that the potency of *cis*-4,4'-DMAR to release catecholamines was lower than that observed for *cis*-4-MAR. 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 (Brandt et al., 2014).

TABLE 3

Stimulation of release in rat brain synaptosomes ([a])

Drug	Release at DAT EC_{50} (nM)	Release at NET EC_{50} (nM)	Release at SERT EC_{50} (nM)	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 ([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

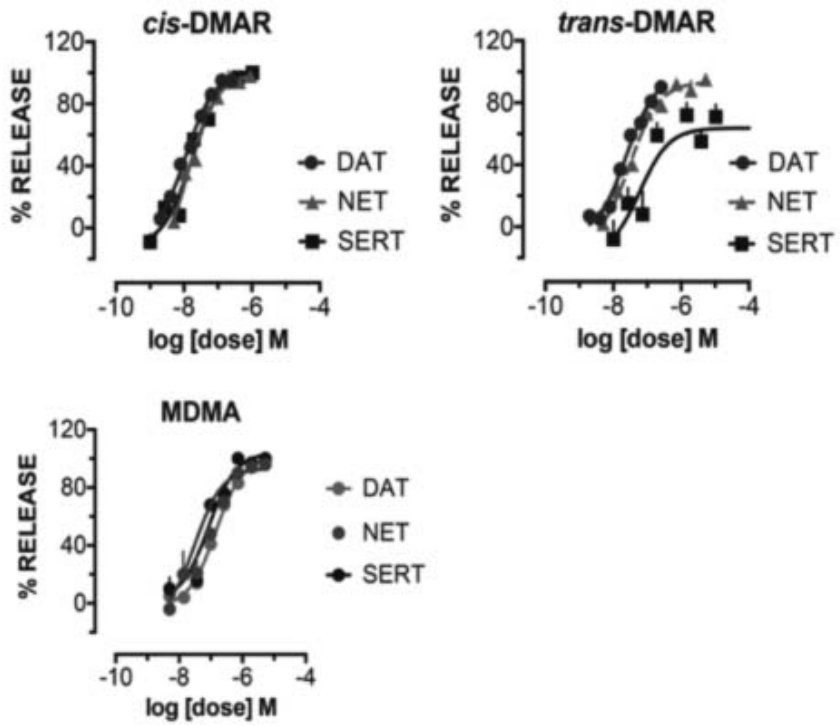
([a]) Table modified from Brandt et al., 2014. DAT: dopamine transporter; NET: norepinephrine transporter; SERT: serotonin transporter; [3H]-1-methyl-4-phenylpyridinium ([3H]MPP+) used as radiolabeled substrate for DAT and NET and [3H]5-HT (serotonin) for SERT. Data expressed as mean ± SD for N = 3–4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

([b]) DAT/SERT ratio calculated by $(EC_{50}$ at DAT$)^{-1}$/ $(EC_{50}$ at SERT$)^{-1}$; higher value = greater DAT selectivity.

([c]) *cis*-4-Methylaminorex racemate.

FIGURE 5

Dose-response effects of *cis*- and *trans*-4,4'-DMAR compared to (*S*)-(+)-3,4-methylenedioxymethamphetamine ((*S*)-(+)-MDMA)) in evoking release from DAT, NET and SERT in rat brain synaptosomes (McLaughlin et al., 2014)



A comparison between *cis*- and *trans*-4,4'-DMAR under identical assay conditions, i.e. monoamine transporter release using rat brain synaptosomes, showed that *trans*-4,4'-DMAR was also a fully efficacious releasing agent at DAT and NET, although slightly less potent than the *cis* isomer (Figure 5, Table 4). The key difference between the *cis* and *trans* isomers was observed at SERT where the *trans* isomer acted as an uptake blocker, which indicated that *trans*-4,4'-DMAR displayed a 'hybrid' profile of a catecholamine releaser with 5-HT uptake blocking properties (McLaughlin et al., 2014). The extent to which some pharmacological overlaps between 4,4-DMAR and MDMA might translate to psychopharmacological overlap in humans has not been investigated.

TABLE 4

Stimulation of release in rat brain synaptosomes ([a])

Drug	Release at DAT EC_{50} (nM)	Release at NET EC_{50} (nM)	Release at SERT EC_{50} (nM)	DAT/SERT ratio ([c])
(*S*)-(+)-MDMA ([b])	143 ± 16	98.3 ± 15.0	85.0 ± 13.3	0.6
***cis*-4,4'-DMAR**	10.9 ± 0.7	11.8 ± 2.0	17.7 ± 2.3	1.6
***trans*-4,4'-DMAR**	24.4 ± 2.7	31.6 ± 4.6	59.9 ± 17.2 ([d])	2.5

([a]) Table modified from McLaughlin et al. (2014). DAT: dopamine transporter; NET: norepinephrine transporter; SERT: serotonin transporter; [^{3}H]-1-methyl-4-phenylpyridinium ([^{3}H]MPP+) used as radiolabeled substrate for DAT and NET and [^{3}H]5-HT (serotonin) for SERT. Data expressed as mean ± SD for N = 3-4 experiments performed in triplicate.
([b]) (*S*)-(+)-3,4-Methylenedioxymethamphetamine.
([c]) DAT/SERT ratio calculated by $(EC_{50}$ at DAT$)^{-1}$/ $(EC_{50}$ at SERT$)^{-1}$; higher value = greater DAT selectivity.
([d]) Fully efficacious as an uptake blocker at SERT and indication that it may not act as substrate-type releaser.
Note: In this follow-up study to Brandt et al., 2014, (S)-(+)-3,4-methylenedioxymethamphetamine ((S)-(+)-MDMA)) was employed as the control, which reflected the fact that this substance is a well-characterised, non-selective substrate-type releaser (Baumann et al., 2007), which was consistent with the data reported in Figure 5 and Table 4. All three test compounds were shown to be non-selective, with DAT/SERT ratios of 0.6 for MDMA, 1.6 for cis-4,4'-DMAR and 2.5 for trans-4,4'-DMAR (McLaughlin et al., 2014).

Pharmacokinetics

Published pharmacokinetic data for 4,4'-DMAR in animals or humans are not available. A report published on the *in vivo* metabolism of 4-methylaminorex (4-MAR) in Sprague-Dawley rats following a single oral and intravenous administration (10 mg/kg) revealed the identification of three metabolites in urine. In addition to the parent molecule 4-MAR (major constituent), the oxazolidinone derivative (oxidative deamination), *para*-hydroxylated 4-MAR and norephedrine were detected (Henderson et al., 1995). It is conceivable therefore that in the case of 4,4'-DMAR detection of the ring-opened, *para*-methylated norephedrine-type counterpart may also be expected. It is worth noting that this latter analyte has also been detected as a mephedrone metabolite (Meyer et al., 2010). More recent work published on the conversion of all stereoisomers of *cis*- and *trans*-4-MAR to their norephedrine/norpseudoephedrine metabolites (adult male Han/Wistar rats; intravenous, intraperitoneal, and oral routes of administration at 2 mg/kg) confirmed differences in pharmacokinetic parameters and tissue distribution. Interestingly, the *trans*-(4*R*,5*R*)-isomer differed significantly from the remaining isomers as it displayed high oral bioavailability and more than a 3-fold longer elimination half-life (Meririnne et al., 2004). Details on the potential for stereospecific pharmacokinetics related to 4,4'-DMAR have not been described.

Interactions with other substances

Given the current lack of data, it is difficult to predict with accuracy any 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 effect 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 and cocaine) may increase the risk of developing serotonergic toxicity (often also referred to as serotonin syndrome), the symptoms of which can include tachycardia, hypertension, hyperthermia, muscle rigidity and convulsions (Boyer and Shannon, 2005; Isbister et al., 2007; Sternbach, 1991). High dosage levels and/or combinations of 4,4'-DMAR with other amphetamine-type substances, e.g. catecholamine releasing agents, 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. The available information related to deaths reported to the EU Early Warning System indicated that in 30 of the 31 deaths one or more psychoactive substances (predominantly stimulants) were present in the analysed biological samples (Section D).

A3. Psychological and behavioural effects

There are no published studies assessing the psychological and/or behavioural effects of 4,4'-DMAR. Self-reported experiences of 4,4'-DMAR use from user websites note a range of effects that include: euphoria, change in visual perception, mental and physical stimulation, empathic effects, nausea, agitation and anxiety.

It is important to note that it is not possible to confirm the specific substance(s) used, nor the purity, dose/amount, etc., in respect of self-reported cases. Analyses of new psychoactive substances or products containing them that are sold on the drug market have shown that the composition can differ from that claimed by the retailer, and can vary over geographical areas and time. Furthermore, the users' physical characteristics and health status are rarely reported. In addition, the information on user websites should be regarded as illustrative only and not taken as representative of users of 4,4'-DMAR in general. Consequently, these reports should be interpreted with caution.

A4. Legitimate uses of the product

4,4'-DMAR and the corresponding enantiomers are expected to become available as an analytical reference standard for use in scientific research and forensic applications. A range of isomers and closely related derivatives/analogues ([28]) have been featured in a number of patent applications filed by the pharmaceutical company Hoffmann-La Roche, which describe their uses as ligands for the trace amine associated receptor 1 (TAAR1) related to a range of potential applications to central nervous system disorders (Decoret et al., 2010; Galley et al., 2008). 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 (e.g. Takagi et al., 2003), thus giving rise to the associated CAS number shown in Table 2. The remaining three forms have not yet been encountered in the existing scientific and patent literature.

There are currently no other indications that 4,4'-DMAR may be used for other legitimate purposes. There are no known uses of 4,4'-DMAR as a component in industrial, cosmetic or agricultural products. There is no information that 4,4'-DMAR is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a European Union database on the synthetic routes of all medicinal products this information cannot be confirmed. There is no marketing authorisation (existing, ongoing or suspended) for 4,4'-DMAR neither in the European Union nor in the Member

([28]) Example: (4*R*)-5,5-dimethyl-4-phenyl-4,5-dihydro-1,3-oxazol-2-amine or 4-ethyl-4-phenyl-4,5-dihydro-1,3-oxazol-2-amine.

States that responded to the request for information from the European Medicines Agency (EMCDDA and Europol, 2014).

Section B. Dependence and abuse potential

B1. Animal in vivo and in vitro data

There are no published animal studies that have examined the dependence and abuse potential of 4,4'-DMAR.

B2. Human data

There are no published studies investigating the dependence and/or abuse potential of 4,4'-DMAR in humans. In addition, there are no published case reports describing the potential for dependence or abuse potential for 4,4'-DMAR. No information is available from drug treatment agencies about the dependence and abuse potential. It was not possible to ascertain the dependence-producing properties or the abuse potential associated with 4,4'-DMAR from user websites.

Section C. Prevalence of use

Information from seizures, collected and biological samples

The first official notification of 4,4'-DMAR to the EU Early Warning System was on 10 December 2012 by the Netherlands national focal point. The Reporting Form details a seizure of 500 g of white powder seized on 19 November 2012 by customs authorities at Amsterdam. The importation was noted to have arrived from India.

Information provided to Europol

Europol received reports from four Member states with regards to 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 (customs authorities in Helsinki), which arrived in a parcel coming from the United Kingdom. This seizure was also reported by the Finnish national focal point to the EMCDDA on 2 July 2013.

Hungary reported that 4,4'-DMAR had been used to make tablets, and that this tableting was presumably carried out in Hungary, but further details were not available. A total of 78 seizures were reported by police between June and October 2013. 4,4'-DMAR was seized as tablets (41 seizures) and in powder form (37 seizures). 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. Quantities of seized powder 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, 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) (see footnotes in Section A1.1). The EMCDDA received the same information from the Hungarian national focal point. In the majority of cases powdered samples were white, but the presence of pink, green and blue powder has also been reported. Tablets have been observed to appear in different colours and in specific shapes, or bearing specific logos such as 'Playboy', 'Heart', 'Mitsubishi', 'Star' and 'Transformers' (EMCDDA and Europol, 2014). According to Hungarian authorities, the number of seizures related to 4,4'-DMAR significantly decreased after the introduction of control measures.

As noted above, the Netherlands reported the first detection of 4,4'-DMAR in December 2012. 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 (and misspelled) as: '4,5-DYHYDRO-4-METHYL-5(-4-METHYLPHENYL)-2-OXAZOLAM'.

In Romania, 4,4'-DMAR was identified in 14 seizures. In 13 cases the substance was seized as a white powder, having a total weight of 564.23 g. In the other case 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.

No reports were received that indicated licit or illicit production of 4,4'-DMAR in any of the Member States, Turkey and Norway. 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 of the site, conducted by the Netherlands Forensic Institute, demonstrated that both MDMA via the bromosafrole route and piperonyl methyl ketone PMK (3,4-methylenedioxyphenylpropan-2-one) via the Wacker method had been produced. Several different types of substances, chemicals and recipes were also found. In addition, two white plastic trays were found containing a few hundred grams of white powder which was found to contain 4-MAR. Moreover, according to the forensic examination, the 4-MAR was 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 illicit drug-producing criminal groups in the European Union.

Information provided to the EMCDDA

The EMCDDA has received reports of detections of 4,4'-DMAR ([29]) from nine Member States (Denmark, Finland, France, Hungary, the Netherlands, Poland, Romania, Sweden and the United Kingdom).

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 (Section A1.2).

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 90 kg of powder ([30]). 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, and Hungary reported a total of 78 seizures.

France reported the identification of 4,4'-DMAR in a white powder (604 mg), which appears to have been sold as MDMA; the investigation is ongoing.

As noted, the Netherlands reported the first seizure of 4,4'-DMAR to the EMCDDA in December 2012. In addition, during 2013 customs authorities in the Netherlands detected a further 90 kg ([30]) of 4,4'-DMAR. No further details are available regarding these cases.

Romania reported 13 seizures made by police in 2013. These comprised one case of five tablets and 12 cases involving powder (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 a number of seizures by police in Northern Ireland, amounting to 608 tablets. This included three cases of 357 tablets that bore a 'cherries' logo and one case of 91 tablets that bore a 'cross' logo (EMCDDA and Europol, 2014). In addition, five plastic bags containing white powder (a total amount of 1.81 g) were recovered by police in Scotland in April 2014 during the investigation of a death related to 4,4'-DMAR (Case 29, Table 5). It was reported that the deceased had not intended to obtain 4,4'-DMAR, but instead they had possibly wished to obtain mephedrone or ketamine.

Biological samples

Three Member States (Hungary, Poland and the United Kingdom) reported detections of 4,4'-DMAR in biological samples from 31 deaths (eight in Hungary; one in Poland; 22 in the United Kingdom) and one non-fatal intoxication (Poland) (Section D1.2.3). Hungary also reported the detection of 4,4'-DMAR in biological samples taken in 18 criminal cases related to the suspected consumption of narcotics.

Collected samples

The United Kingdom reported the detection of 4,4'-DMAR in a collected sample. A 5 g sample was purchased for GBP 60 (EUR 73) from an Internet retailer ([31]) in March 2014. The product was a white powder, labelled '5 g' '4,4'-DMAR' (EMCDDA and Europol, 2014). Analysis revealed the presence of *cis*-4,4'-DMAR as the hydrochloride salt. No additional constituents were detected (Brandt et al., 2014).

([29]) '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 from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).

([30]) This figure was given as '260 kilograms' in the Joint Report (EMCDDA and Europol, 2014); however, the Netherlands national focal point informed the EMCDDA that the correct total quantity seized was around 90 kg.

([31]) www.chems-direct.org. It is noteworthy that the price of 4,4'-DMAR has dropped on this website since purchase in late March 2014 (e.g. as of 19 April 2014: EUR 40 for 5 g). At the time of writing (21 August 2014), the website was 'unavailable due to maintenance'.

Availability from Internet retailers

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). The second site offered 4,4'-DMAR in powder form; further details, including on the quantities available and price, were only available on application to the site. Four retailers were identified who appear to have discontinued the sale of 4,4'-DMAR; the reasons for the apparent discontinuation of the sale of this substance were not provided. An earlier study undertaken in April 2014 identified one Internet site selling 4,4'-DMAR with similar reduction in price per gram with increasing purchase quantities (Nizar et al., 2014). This study identified 20 Internet sites selling 4-MAR. Based on this data it would appear that the availability of 4,4'-DMAR from Internet retailers is limited.

Prevalence of use

There are currently no coordinated national or European surveys on the prevalence of use of 4,4'-DMAR in the general population or in targeted populations. Further, neither the European School Survey Project on Alcohol and Other Drugs (ESPAD) nor other school/college/university surveys have investigated or reported on 4,4'-DMAR use. Information from seizures and deaths (Section D1.2.3) reported by the Member States suggests that in some cases 4,4'-DMAR is sold as ecstasy and other illicit drugs, although the extent of this is unknown.

Information from poison information services

The National Poisons Information Service in the United Kingdom, which provides information on the number of accesses to information held on its online poisons information database TOXBASE® and details of telephone enquiries made to the service by health professionals, reported eight accesses to TOXBASE® between 12 February and the end of June 2014, which indicates that the need for access to information with regards to this particular substance has been limited ([32]).

([32]) There have been two telephone enquiries involving the use of a product termed 'Euphoria' and its involvement in adverse reactions (including agitation and pyrexia). As noted in Section A1.1, the term 'Euphoria' was used as a street name for 4-methylaminorex. Further information, for example analytical confirmation or whether 'euphoria' was a branded product sold as a new psychoactive substance, is unavailable.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

No studies were identified that have investigated the adverse events and acute toxicity of 4,4'-DMAR in animal models.

D1.2. Human data

No clinical studies were identified that have examined the adverse events and acute toxicity of 4,4'-DMAR in humans.

D1.2.1. User reports

There are few self-reported user experiences on user websites that discuss the subjective effects of 4,4'-DMAR ([33]), including adverse effects. The number of posts that describe detailed experiences with the substance is more limited, as compared to more established psychostimulants and 'research chemicals'. There is a need to interpret these user reports with caution since there was no analytical confirmation of the substances used (see caveat in Section A3). In addition, some of the users describe taking other drugs prior to or with 4,4'-DMAR.

The onset is described as being noticed within 10 to 60 minutes, although it appears to take longer in some individuals, thus possibly leading to re-dosing while waiting for the initial effects to be noticed ([34]). Effects appear to last several hours ([35,36]) and increases in heart rate and body temperature have been noted ([37]). 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 ([38]).

The French national focal point provided information that noted recommendations from users on French language user

([33]) For example, ukchemicalresearch.org, 2014; drugs-forum.com, 2014; chemsrus.com, 2014.
([34]) www.chemsrus.com/forum/14-trip-reports/37810-serotoni-repeated-dosing-familiar-feel (21 August 2014).
([35]) www.drugs-forum.com/forum/showthread.php?t=216908 (August 2014).
([36]) www.zoklet.net/bbs/showthread.php?t=289735 (August 2014).
([37]) www.bluelight.org/vb/threads/676724-4-4-Dimethylaminorex-(4-5-dihydro-4-methyl-5-(4-methylphenyl)-2-Oxazolamine) (15 August 2014).
([38]) www.ukchemicalresearch.org/Thread-Serotoni-Powder-Serotonin-Syndrome-and-Stimulant-Psychosis (August 2014).

websites to avoid 'any other products and specifically serotoninergic [*sic*] products at least 4 days before and after tacking [*sic*] product'. It was also noted that users who may have developed tolerance to stimulants may require longer time periods before noticing the effects (> 1.5 hours). The 'comedown' period has been described to be long lasting, up to 12 hours. Undesired after-effects were perceived to be less demanding than those experienced with MDMA if appropriate dosage regimes were followed.

D1.2.2. 4,4'-DMAR associated acute toxicity

Since October 2013 a total of 32 serious adverse events ([39]) associated with 4,4'-DMAR have been reported to the EU Early Warning System. Of the 32 cases, one was a non-fatal intoxication and 31 were deaths. The presence of 4,4'-DMAR was analytically confirmed in all 32 cases.

Poland reported the preliminary details of a non-fatal intoxication, which occurred in September 2013. A 16-year-old female was admitted to hospital with suspicion of intoxication with 'legal highs'. Based on information from witnesses, she had been smoking an unknown herbal mixture after which she felt ill, collapsed and vomited. On admission to hospital the patient was in a generally fair condition, with verbal contact, dilated pupils, blood pressure of 110/70 and heart rate of 89 bpm. The next day alarming symptoms were observed (not further described). A blood sample (further details were not reported) was collected 24 hours after admission and found to contain 0.448 mg/L 4,4'-DMAR. The investigation is currently ongoing.

Information provided by Member States related to 4,4'-DMAR associated deaths (also involving other substances) note a number of adverse effects, including: agitation, hyperthermia, convulsions, breathing problems and cardiac arrest (Section D1.2.3).

D1.2.3. 4,4'-DMAR associated deaths

A total of 31 deaths associated with 4,4'-DMAR were reported by Hungary (eight deaths), Poland (one death) and the United Kingdom (22 deaths) ([40]). The deaths in Hungary occurred between June and October 2013, the Polish death in July 2013 and those in the United Kingdom between June 2013 and June 2014. The cause of death has not yet been reported for most of the cases. Table 5 provides the available details on these cases.

Data on gender and age were available for 30 of the decedents. Twenty-two were males aged between 18 and 41 (four from Hungary; the deceased from Poland; 17 from the United Kingdom) and eight were females aged between 16 and 43 years (four from Hungary; four from the United Kingdom).

4,4'-DMAR was detected in post-mortem biological samples in all 31 deaths. 4,4'-DMAR was quantified in 26 of the deaths, with concentrations ranging from less than 0.02 mg/L to 18.68 mg/L in blood, and from 5.93 mg/L to 43.49 mg/L in urine. In all apart from one case, other stimulants (including cocaine, amphetamines and new psychoactive substances such as synthetic cathinones) were also found (Table 5).

In an attempt to evaluate the toxicological significance of 4,4'-DMAR in the deaths reported, an assessment of the following evidence was considered in each case: presence and concentration (and pharmacological nature) of 4,4'-DMAR; presence and concentration (and pharmacological nature) of other drugs present (including alcohol); circumstances of death; pathological findings at post-mortem, and cited cause of death. This allowed categorisation of the significance of 4,4'-DMAR in the deaths as being of low significance (i.e. alternative cause of death), medium significance (i.e. 4,4'-DMAR may have contributed to toxicity/death but other drugs present may have been more toxicologically significant) or high significance (i.e. 4,4'-DMAR was cited as the cause of death or was assessed to have been likely to contribute to toxicity/death even in the presence of other drugs). In order to highlight potential interactions or contributing toxicology, the other substances found in the cases were characterised.

The results of this assessment concluded that in 23 deaths 4,4'-DMAR was either the cause of death (three cases) or is likely to have contributed to death (20 cases) even in the presence of other substances; in one of these deaths 4,4'-DMAR was the sole drug present. In eight 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.

([39]) Serious adverse event means any adverse event associated with the consumption of a new psychoactive substance in a human that: results in death; is life-threatening; requires hospitalisation; results in persistent or significant disability or incapacity; consists of a congenital anomaly or birth defect; or is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also be considered serious. Examples of such events are intensive treatment in an emergency room; convulsions that do not result in hospitalisation; or the development of substance dependency or substance abuse. This definition was adapted from the guidelines of ICH (1994).

([40]) Eighteen of the deaths from the United Kingdom have been formally published as a case series to alert the scientific community about the presence of 4,4'-DMAR on the illicit drug market (Cosbey, et al., 2014).

TABLE 5
Deaths associated with 4,4'-DMAR reported to the EU Early Warning System

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	June 2013	25	M	Blood[f]	1.158 mg/L	7-Amino-clonazepam 0.1405 mg/L alpha-PVP 0.0056 mg/L Pentedrone 0.0274 mg/L	High body temperature, huge 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 Pentedrone 15.276 mg/L		
2	HU	June 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, huge bleeding in the muscles, and organs. Confusion, disorientation, unconsciousness, perspiration.	Injected, use about 3pm, 12 hours later died in the hospital.
3	HU	June 2013	18	M	Blood[u]	+ (no quantitation)	Mephedrone (no quantitation) MDMA (no quantitation) Pentedrone (no quantitation)	Myoclonus, unconsciousness, body temperature: 42.9°C, internal bleeding (oral, intestinal), cardial and respiratorical 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, he died the next morning.
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, 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	Sept 2013	20	F	Blood[f]	3.565 mg/L	Alprazolam 0.0951 mg/L alpha-PVP 0.0296 mg/L Pentedrone 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	Pentedrone 44.544 mg/L Amphetamine 0.353 mg/L alpha-PVP 0.0844 mg/L Alprazolam 0.0167 mg/L		
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 one hour she died. (Arrived: 23:05, died: 00:04.)

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
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 the 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 oedema, pulmonary oedema, tonsillar herniation, emollient brain tissue	—
9	PL	July 2013	34	M	Blood[u]	0.679 mg/L	*N*-Ethylbuphedrone 0.341 mg/L Midazolam 0.052 mg/L alpha-hydroxymidazolam 0.035 mg/L	Admitted to hospital deeply unconscious, breathing on his own, with no reaction to sensory stimulation, fixed dilated pupils, increased muscle tonus, muscle tremor, spasm of the jaw muscles, bruising around lips and ears, blood pressure 70/30 and pulse 140. Patient was intubated and gastric lavage was performed. Patient died of cardiac arrest. Resuscitation was ineffective.	Male was found unconscious and with seizures in his room at 3.00 p.m. He had been seen the previous evening. In his room, a number of empty packages were found with the following labels: NEB (5 packages), 3,4 DMMC (2 packages), pentedrone (6 packages), MDAI (1 package), 5-APB (1 package), bufedrone (3 packages), Eth-Cat (4 packages) , MDEC (1 package), 3-MMC (1 package), IGNITE (10 packages), 4-FMA (1 package), MXE (1 package), ethylphenidate (2 packages), alpha-PVP (1 package) and 4,4 DMAR (1 package).
10	UK	Jun 2013	36	M	Blood[f]	0.66 mg/L	Benzoylecognine 0.97 mg/L Cocaine <0.05 mg/L Codeine <0.02 mg/L Tetra/levamisole (unconfirmed)	—	—
11	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 'methadrone', continued drinking, took 2 'ecstasy' tabs immediately felt unwell, agitated. Unresponsive 1 hour later.
12	UK	Jun 2013	33	M	Blood[f]	0.28 mg/L	Benzoylecognine 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.
13	UK	Jun 2013	27	M	Blood[f]	0.7 mg/L	Benzoylecognine 0.36 mg/L MDMA 0.19 mg/L MDA Mirtazapine (a low level) Indications of low level of cocaine	—	4,4'-DMAR detected with cocaine on nasal swabs. 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
14	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.
15	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.
16	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.
17	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.
18	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"'.
19	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.
20	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 taken 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.

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
21	UK	Sep 2013	31	M	Blood[f]	1.72 mg/L	Benzoylecognine 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.
22	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.
23	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.
24	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 pregabalin	—	History of drug misuse, overdoses and mental illness.
25	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'.
26	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.
27	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.
28	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.

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
29	UK	April 2014	19	F	Blood	~1mg/L (*cis*-isomer confirmed) (no certified reference material so not reported quantitatively)	None detected	Became agitated and collapsed, high temperature (38.9oC)	Deceased believed she had taken 'MCAT' (mephedrone). CPR performed by friends at the scene until paramedics took over. Witnesses uncooperative with police regarding drug use. cis-4,4'-DMAR was stated as the cause of death.
30	UK	June 2014	29	M	Blood[f]	1.68 mg/L	MDMA 0.69 mg/L Ethylphenidate (low conc.), cocaine (low conc.)	Significant body stiffness was observed.	Collapsed in garden and believed to have taken 'Miaow' (note: name often associated with mephedrone). Cause of death was reported as MDMA and 4,4'-DMAR toxicity.
31	UK	June 2014	27	M	Blood[f]	18.68 mg/L	Mephedrone 15.73 mg/L Cocaine 0.46 mg/L Benzoylecognine > 2mg/L Levamisole (low conc.) Hydroxyzine (low conc.)	Reported to be twitchy and sweating. Significant body rigidity was observed.	Collapsed and believed to have taken cocaine. Cause of death reported as cocaine, mephedrone and 4,4'-DMAR toxicity.

Key:
MS: Member State; HU: Hungary; PL: Poland; UK: United Kingdom; M: male; F: female; Blood[f]: femoral blood sample; Blood[u]: site of blood sample unspecified; –: not reported.

D2. Chronic health effects

D2.1. Animal data

There are no published studies investigating the chronic health effects of 4,4'-DMAR in animals.

D2.2. Human data

There are no published studies investigating the chronic health effects of 4,4'-DMAR in humans.

D3. Factors affecting public health risks

D3.1. Availability and quality of the new psychoactive substance on the market

4,4'-DMAR is sold as a drug in its own right and offered for sale by Internet retailers and in both retail and wholesale quantities. It has been sold as a 'research chemical' and in octagonal tablets with the markings 'ST' and '60' called 'Serotoni'. In comparison to many other more commonly advertised new psychoactive substances or 'research chemicals', it also appears that the number of Internet retailers that offer this particular substance is limited (Section C).

Information from seizures and deaths associated with 4,4'-DMAR reported by Member States indicates that 4,4'-DMAR has also been sold as ecstasy and other illicit drugs. Seized street tablets found to contain 4,4'-DMAR showed a range of markings and logos ([41]), raising the likelihood that these particular products were designed to be sold as 'ecstasy' tablets on the illicit drug market.

D3.2. Availability of information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects

Relative to other more commonly advertised new psychoactive substances or 'research chemicals', there appears to be limited information on popular user websites regarding the effects and potential health/adverse effects related to the use of 4,4'-DMAR (Section D1.2.1). At the time of writing ([42]), no entry in the 'Erowid Experience Vaults' ([43]) could be identified. The users and forum discussion participants appear to be generally aware of the stimulant-type (wanted and unwanted) effects of this substance.

D3.3. Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviour of users of 4,4'-DMAR. There are self-reported user experiences where individuals have posted their experiences with the drug on user websites. In cases where 4,4'-DMAR is sold surreptitiously as part of 'ecstasy'-type tablet formulations or other illicit drugs, it appears likely that these may be taken within environments that may extend beyond home use, such as clubbing situations, etc. Information from the United Kingdom relating to deaths associated with 4,4'-DMAR indicated a pattern of use to be 'house party type environment, in combination with other drugs, such as cocaine, "ecstasy" type drugs, substituted cathinones, diazepam and cannabis'.

D3.4. Nature and extent of health consequence

The limited information on the acute health effects of 4,4'-DMAR was discussed in Section D1.2. There is insufficient information in the reported deaths where 4,4'-DMAR has been detected to discuss in detail the circumstances of these cases and the potential impact on road traffic accidents or psychological functioning.

D3.5. Long-term consequences of use

As noted in Sections D2.1 and D2.2, there are no animal or human data on the chronic health effects of 4,4'-DMAR use.

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

As noted, it appears that the sourcing and use of 4,4'-DMAR can be related to either individuals attempting to source the drug itself from online sources, for example as a 'research chemical'. In other cases it has been sold/provided surreptitiously as ecstasy or other illicit drugs. It is likely that 4,4'-DMAR is used in the same environments as other stimulant-type drugs. This would be typically (but not restricted to) home environments (Section D3.3), discotheques/nightclubs and outdoor music festivals.

([41]) 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.
([42]) 15 August 2014.
([43]) Users have the opportunity to submit their experiences and 'trip reports' to this drug information website: www.erowid.org/experiences/exp_front.shtml.

Section E. Social Risks

E1. Individual social risks

No data are available to determine the impact of 4,4'-DMAR in this area.

E2. Possible effects on direct social environment

No data are available to determine the impact of 4,4'-DMAR in this area.

E3. Possible effects on society as a whole

No data are available to determine the impact of 4,4'-DMAR in this area.

E4. Economic costs

No data are available to determine the impact of 4,4'-DMAR in this area.

E5. Possible effects related to the cultural context, for example marginalisation

No data are available to determine the impact of 4,4'-DMAR in this area.

E6. Possible appeal of the new psychoactive substance to specific population groups within the general population

No data are available to determine the possible appeal of 4,4'-DMAR to specific population groups within the general population.

Section F. Involvement of organised crime

F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain

Limited information is available from the 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 illicit drug-producing criminal groups in the European Union.

F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances

Based on the information available it does not appear that the production, trafficking and distribution of 4,4'-DMAR impacts on other existing psychoactive substances or new psychoactive substances.

F3. Evidence of the same groups of people being involved in different types of crime

No information has been received by Europol of evidence of the same groups of people being involved in different types of crime in connection with 4,4'-DMAR.

F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)

No information has been received by Europol on incidents of violence in connection with 4,4'-DMAR.

F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society

No information has been received by Europol on incidents of money laundering or the impact of organised crime on other socioeconomic factors in society in connection with 4,4'-DMAR.

F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)

No data are available to determine the impact of 4,4'-DMAR in this area.

F7. Use of violence between or within criminal groups

No information has been received by Europol on incidents of violence in connection with 4,4'-DMAR.

F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation

No information has been received by Europol on strategies to prevent prosecution in connection with 4,4'-DMAR.

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Council Decision

COUNCIL IMPLEMENTING DECISION (EU) 2015/1873 of 8 October 2015 on subjecting 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-DMAR) and 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) to control measures

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances ([1]), and in particular Article 8(3) thereof,

Having regard to the proposal of the European Commission,

Having regard to the opinion of the European Parliament,

Whereas:

(1) A Risk Assessment Report on the new psychoactive substance 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2- amine (4,4'-DMAR) was drawn up in accordance with Article 6 of Decision 2005/387/JHA by a special session of the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and was subsequently submitted to the Commission and to the Council on 19 September 2014.

(2) 4,4'-DMAR is a synthetic substituted oxazoline derivative. It is a derivative of aminorex and 4-methylaminorex (4-MAR), two synthetic stimulants controlled under the 1971 United Nations Convention on Psychotropic Substances.

(3) 4,4'-DMAR has been available on the drugs market in the Union since at least December 2012 and was notified to the Early Warning System in December 2012. Nine Member States have reported detections as a result of seizures of the substance, mainly in the form of white or coloured powders and tablets, as well as biological and collected samples.

(4) 4,4'-DMAR emerged on the new psychoactive substances market as a 'research chemical' sold by internet retailers, and it is now available on the street market. 4,4'-DMAR is being sold and consumed as a substance on its own, but it has also been mis-sold on the illicit market as ecstasy and amphetamines.

(5) There have been 31 deaths associated with 4,4'-DMAR registered in three Member States, between June 2013 and June 2014. In most cases, 4,4'-DMAR was either the cause of death or, together with other substances, is likely to have contributed to death. One Member State has reported a case of non-fatal intoxication.

(6) There are no studies on the toxicity of 4,4'-DMAR.

(7) There is no prevalence data on the use of 4,4'-DMAR. However, the information available suggests that it has not been widely used. Information obtained from cases

([1]) OJ L 127, 20.5.2005, p. 32.

involving death also suggests that users unknowingly consumed 4,4'-DMAR when seeking other stimulants.

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

(9) 4,4'-DMAR is not listed for control under the 1961 United Nations Single Convention on Narcotic Drugs or under the 1971 United Nations Convention on Psychotropic Substances. It is not currently under assessment, and has not been under assessment, by the United Nations' system, and no such assessment is planned.

(10) 4,4'-DMAR has no established or acknowledged human or veterinary medical use in the Union. Apart from its use in analytical reference materials, and in scientific research investigating its chemistry, pharmacology and toxicology, there is no indication that it is being used for other purposes.

(11) The Risk Assessment Report reveals that there is limited scientific evidence available on 4,4'-DMAR and points out that further research would be needed to determine the health and social risks that it poses. However, the evidence and information currently available provides sufficient ground for subjecting 4,4'-DMAR to control measures across the Union. As a result of the risks to health that the consumption of 4,4'-DMAR poses, as documented by its detection in several fatalities, of the fact that users may unknowingly consume it, and of the lack of medical value of this substance, 4,4'-DMAR should be subjected to control measures.

(12) Given that three Member States control 4,4'-DMAR under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances and five Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would protect against the risks that its availability and use can pose.

(13) A Risk Assessment Report on the new psychoactive substance 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) was drawn up in accordance with Article 6(2), (3) and (4) of Decision 2005/387/JHA by a special session of the extended Scientific Committee of the EMCDDA, and was subsequently submitted to the Commission and to the Council on 6 October 2014.

(14) MT-45 is an *N,N'*-disubstituted piperazine, having a cyclohexane ring attached to one of the nitrogen atoms of the piperazine ring and a 1,2-diphenylethyl moiety attached to the other nitrogen atom. MT-45 is one of a series of 1-(1,2-diphenylethyl)piperazine analgesics invented in the early 1970s.

(15) MT-45 has been present on the drugs market in the Union since October 2013, where it is sold as a 'research chemical', mostly on the internet. The EMCDDA has identified 12 sites of internet suppliers and retailers that have offered MT-45 for sale, including some apparently based in the Union.

(16) A total of 28 fatalities occurring between November 2013 and July 2014 have been reported by one Member State. In most cases, the presence of MT-45 in biological samples was analytically confirmed. Some 18 non-fatal intoxications have also been reported by the same Member State, the clinical features of which were similar to opioid intoxication, responding in some cases to the opioid receptor antagonist naloxone.

(17) There are several studies in animals indicating that the acute toxicity of MT-45 is several-fold higher than that of morphine.

(18) Currently available information suggests that MT-45 has not been widely used. The substance appears to be mostly used in the home environment either by users willing to try a new substance or by opioid dependent users with no access to heroin or any other opioid. Users may combine MT-45 with other psychoactive substances. There is no information on the social risks that may be related to MT-45.

(19) There is no evidence of involvement of organised crime in the manufacture, distribution, trafficking and supply of MT-45 in the Union. The chemical precursors and the synthetic routes used to manufacture the MT-45 detected in Member States are unknown.

(20) MT-45 is not listed for control under the 1961 United Nations Single Convention on Narcotic Drugs or under the 1971 United Nations Convention on Psychotropic Substances. It is not currently under assessment, and has not been under assessment, by the United Nations' system, and no such assessment is planned.

(21) MT-45 has no established or acknowledged human or veterinary medical use in the Union. Apart from its use in analytical reference materials, and in scientific research investigating its chemistry, pharmacology and toxicology, there is no indication that it is being used for other purposes.

(22) The Risk Assessment Report reveals that there is limited scientific evidence available on MT-45 and points out that further research would be needed to determine the health and social risks that it poses. However, the evidence and information currently available provides sufficient grounds for subjecting MT-45 to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several fatalities, and of the lack of medical value of this substance, MT-45 should be subjected to control measures.

(23) Given that one Member State controls MT-45 under national legislation complying with the obligations under the 1961 United Nations Single Convention on Narcotic Drugs and under the 1971 United Nations Convention on Psychotropic Substances and seven Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would protect against the risks that its availability and use can pose.

(24) Decision 2005/387/JHA confers upon the Council implementing powers with a view to giving a quick and expertise-based response at Union level to the emergence of new psychoactive substances detected and reported by the Member States, by subjecting those substances to control measures across the Union. As the conditions and procedure for triggering the exercise of such implementing powers have been met, an implementing decision should be adopted in order to put 4,4'-DMAR and MT-45 under control across the Union.

(25) Denmark is bound by Decision 2005/387/JHA and is therefore taking part in the adoption and application of this Decision which implements Decision 2005/387/JHA.

(26) Ireland is bound by Decision 2005/387/JHA and is therefore taking part in the adoption and application of this Decision which implements Decision 2005/387/JHA.

(27) The United Kingdom is not bound by Decision 2005/387/JHA and is therefore not taking part in the adoption of this Decision which implements Decision 2005/387/JHA and is not bound by it or subject to its application,

HAS ADOPTED THIS DECISION:

Article 1

The following new psychoactive substances shall be subjected to control measures across the Union:

(a) 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-DMAR);

(b) 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45).

Article 2

By 21 October 2016, Member States shall take the necessary measures, in accordance with their national law, to subject the new psychoactive substances referred to in Article 1 to control measures and criminal penalties, as provided for under their legislation complying with their obligations under the 1961 United Nations Single Convention on Narcotic Drugs and/or under the 1971 United Nations Convention on Psychotropic Substances.

Article 3

This Decision shall enter into force on the day following that of its publication in the *Official Journal of the European Union*.

This Decision shall apply in accordance with the Treaties.

Done at Luxembourg, 8 October 2015.

For the Council
The President
J. ASSELBORN

Abbreviations	
(R)	Levorotatory *(rectus)*
(S)	Dextrorotatory *(sinister)*
3,4-DMMC	3,4-Dimethylmethcathinone
3-MMC	3-Methylmethcathinone
4,4'-DMAR	4,4'-dimethylaminorex
4-FMA	4-Fluoromethamphetamine
4-M-4-MAR	4,4'-Dimethylaminorex
4-MAR	4-Methylaminorex
4-MEC	4-Methylethcathinone
4-MMC	4-Methylmethcathinone
5-APB	5-(2-aminopropyl)benzofuran
5-APDB	5-(2-aminopropyl)-2,3-dihydrobenzofuran
5-HT	Serotonin
API	Active pharmaceutical ingredient
BAC	Blood alcohol content
bk-MDMA	bk-Methylenedioxymethamphetamine (Methylone)
bk-MPA	bk-Methylthienylpropamine
Blood^{f}	Femoral blood
Blood^{u}	Unspecified site of blood sample
BrCN	Cyanogen bromide
CAS	Chemical Abstracts Service registry number
CPR	Cardiopulmonary resuscitation
DA	Dopamine
DAT	Dopamine transporter
Decision	Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances
EC_{50}	Half maximal effective concentration
ECHA	European Chemicals Agency
EI/CI	Electron- and chemical ionisation
EI-MS	Electron ionisation–mass spectroscopy
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
ESI	Electrospray ionisation
ESI-MS/MS	Electrospray ionisation tandem mass spectroscopy
ESPAD	European School Survey Project on Alcohol and other Drugs
Eth-Cat	Ethcathinone
EtOH	Ethanol
EU	European Union
EUR	Euro
EWS	Early Warning System (EMCDDA–Europol)
FMC	Fluoromethcathinone

Abbreviations	
FTIR	Fourier transform infrared spectroscopy
GBP	British Pound
GC	Gas chromatography
GC-MS	Gas chromatography–mass spectrometry
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
KOCN	Potassium cyanate
LC	Liquid chromatography
LC-MS	Liquid chromatography–mass spectrometry
LC-MS/MS	Liquid chromatography–tandem mass spectrometry
LD_{50}	Median lethal dose
MCAT	4-Methylmethcathinone (Mephedrone)
MDA	3,4-Methylenedioxyamphetamine
MDAI	Methylenedioxyaminoindane
MDEC	3,4-Methylenedioxyethcathinone (Ethylone)
MDMA	3,4-Methylenedioxymethamphetamine
MPP	1-Methyl-4-phenylpyridinium
MPPP	4'-Methyl-alpha-pyrrolidinopropiophenone
MS	Mass spectrometry
MS	Member State
MXE	Methoxetamine
$NaBH_4$	Sodium borohydride
NE	Norepinephrine
NEB	*N*-Ethylbuphedrone
NET	Norepinephrine transporter
NMR	Nuclear magnetic resonance spectroscopy
p4-DMAR	4,4'-Dimethylaminorex
PMA	*para*-Methoxyamphetamine
PMK	Piperonyl methyl ketone
PMMA	*para*-Methoxymethamphetamine
REACH	Regulation on registration, evaluation, authorisation and restriction of chemicals, database hosted by European Chemicals Agency
RH-34	3-[2-(2-Methoxybenzylamino)ethyl]-1H-quinazoline-2,4-dione
SD	Standard deviation
SERT	Serotonin transporter
SSRIs	Selective serotonin reuptake inhibitors
ST	4,4'-Dimethylaminorex
ST60	4,4'-Dimethylaminorex
TAAR	Trace amine associated receptor
THC-COOH	Tetrahydrocannabinol-carboxylic acid

Abbreviations	
TOXBASE	Clinical toxicology database of the National Poisons Information Service (United Kingdom)
UAC	Urine alcohol content
UN	United Nations
UR-144	(1-Pentyl-1H-indol-3-yl)-(2, 2, 3, 3-tetramethyl-cyclopropyl)methanone
WHO	World Health Organization
α-PVP	α-Pyrrolidinovalerophenone

Participants of the risk assessment meeting, 16 September 2014

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- **Dr István Ujváry,** Budapest University of Technology and Economics, Budapest
- **Dr David Wood,** Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

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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

- Risk assessment of new psychoactive substances — operating guidelines, 2010

EMCDDA and Europol

- EMCDDA–Europol Joint Report on a new psychoactive substance: 4,4'-DMAR, 2014
- EMCDDA–Europol 2013 Annual Report on the implementation of Council Decision 2005/387/JHA, 2014
- EMCDDA–Europol Early-warning system on new psychoactive substances — operating guidelines, 2007

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

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

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