

**para-Methyl-4-methylaminorex
(4,4'-DMAR)**

Critical Review Report

Agenda item 5.5

Expert Committee on Drug Dependence

Thirty-seventh Meeting

Geneva, 16-20 November 2015



**World Health
Organization**

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Summary

4,4'-DMAR is a synthetic stimulant drug existing in four enantiomeric forms and is structurally related to 4-methylaminorex (4-MAR) and aminorex, which are both listed in the 1971 United Nations Convention on Psychotropic Substances. 4,4'-DMAR has been available particularly in Europe since the end of 2012 via websites selling “research chemicals” predominantly in powder form with additional on-line and “street” availability as “Ecstasy-like” tablets. There have been limited published studies but *in vitro* animal studies have shown that cis-4,4'-DMAR is a potent substrate-type releaser at dopamine, norepinephrine and serotonin transporters with comparable potency at dopamine and norepinephrine transporters to that of *d*-amphetamine and aminorex. On the other hand, cis-4,4'-DMAR exerted much more potent actions at SERT when compared to *d*-amphetamine, aminorex and cis-4-MAR. trans-4,4'-DMAR was also found to be a non-selective catecholamine releaser but serotonin uptake inhibitor. Both cis- and trans-4,4'-DMAR were more potent than (S)-(+)-MDMA in its ability to evoke catecholamine release. Over a short period of time it has been associated with one non-fatal intoxication and thirty-two deaths in four countries. Symptoms in users have included agitation, hyperthermia, foaming at the mouth, breathing problems and cardiac arrest but in the large majority of cases other drugs were involved. Nevertheless, no other drugs or drugs that would not be considered to be significantly contributory were found in some of the fatalities. Extrapolated animal studies have indicated both an abuse and dependence potential for 4,4'-DMAR but no human data are available.

1. Substance identification

A. *International Nonproprietary Name (INN)*

None.

B. *Chemical Abstract Service (CAS) Registry Number*

Free base: 364064-08-4

Form not specified: 1445569-01-6

C. *Other Names*

4,4'-DMAR

4-Methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine

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

D. *Trade Names*

None.

E. *Street Names*

4-MAX, McN-822 and 'ICE'. 4,4'-DMAR is predominantly referred as 4,4'-DMAR on the internet "legal high" websites.

F. *Physical properties*

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), respectively. The melting point of a recrystallised cis-4,4'-DMAR hydrochloride salt sample obtained from an Internet retailer was given as 163–165°C (ethyl acetate/methanol).¹ The cis-4,4'-DMAR HCl salt is a white crystalline powder and soluble in water.

G. *WHO Review History*

4,4'-DMAR has not been previously reviewed by WHO.

2. Chemistry

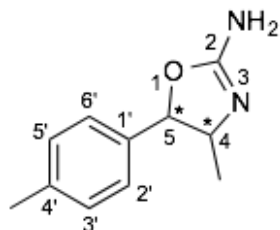
A. Chemical Name

IUPAC Name: 4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine

CA Index Name: Not applicable

B. Chemical Structure

Free base:



Molecular Formula: C₁₁H₁₄N₂O

Molecular Weight: Free base = 190.25

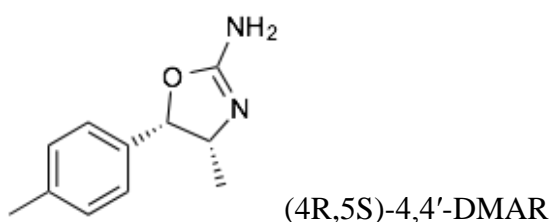
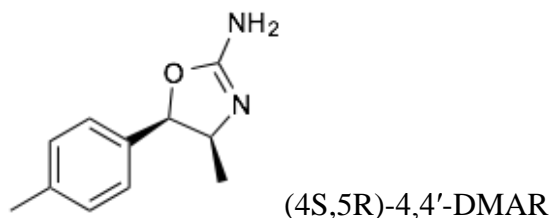
Melting point: 136–138°C (cis-4,4'-DMAR);
101–103°C (trans-4,4'-DMAR);
163–165°C (HCl salt)

Boiling point: Not known

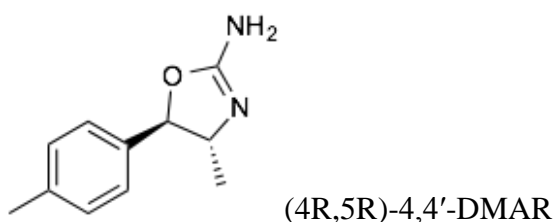
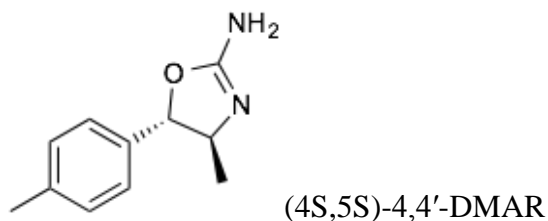
C. Stereoisomers

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

(±)-cis-4,4'-DMAR or (4/SR/,5/RS/)-4,4'-DMAR forms :-



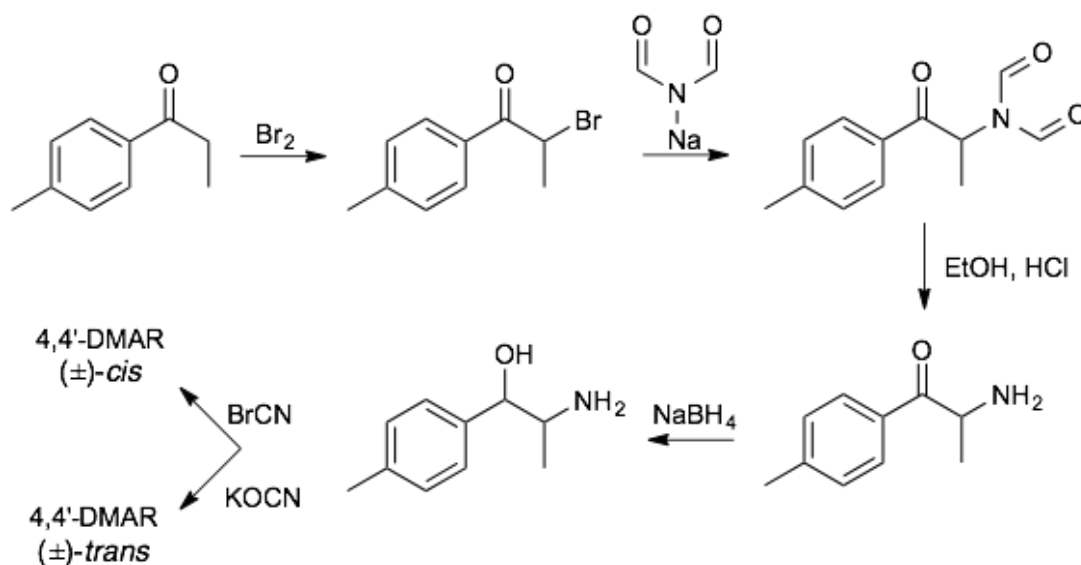
(±)-trans-4,4'-DMAR or (4/SR/,5/SR/)-4,4'-DMAR forms :-



D. Synthesis

Methods of manufacturing:

The synthesis of cis- and trans-4,4'-DMAR has been published and is shown below.¹ 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.^{2,3,4} 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.



E. Chemical description.

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. 4-methylaminorex is listed as a Schedule I substance and aminorex is listed as a Schedule IV substance under the 1971 United Nations Convention on Psychotropic Substances.

F. Chemical properties

See Section B and G

G. Chemical identification

Analytical characterization and preparation of both cis- and trans-4,4'-DMAR racemates have been reported.¹ This includes ¹H and ¹³C 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^{•+}), 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: ¹H NMR (CDCl₃) 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-CH₃) and 0.84 (d, J = 6.8 Hz, 3 H, CH₃); ¹³C NMR (CDCl₃) 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-CH₃) and 17.59 (CH₃).

trans-4,4'-DMAR free base: ¹H NMR (CDCl₃) 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-CH₃) and 1.40 (d, J = 6.2 Hz, 3 H, CH₃); ¹³C NMR (CDCl₃) 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-CH₃) and 20.08 (CH₃).

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.⁵ Data

from these deaths as well as others reported by the United Kingdom, as well as data from a collected sample purchased from an Internet retailer indicate that it is the cis-form of 4,4'-DMAR on the drug market.¹ 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. Also, the preparation and analytical characterisation of the 3,4-dimethylaminorex isomers (both methyl groups present on the oxazoline ring) has been described in the literature⁶ and analytical differentiation from 4,4'-DMAR would be not expected to cause difficulties. One of the trans-enantiomers appears to have been discussed on an online forum and called '4-DMAR' and 'Direx'.

There is no information on presumptive colour tests with 4,4'-DMAR. There are no specific immunoassay tests available, although it may present a presumptive positive finding against amphetamine immunoassay tests.

3. Ease of convertibility into controlled substances

No information available (especially in relation to possible conversation to aminorex).

4. General pharmacology

A. Pharmacodynamics

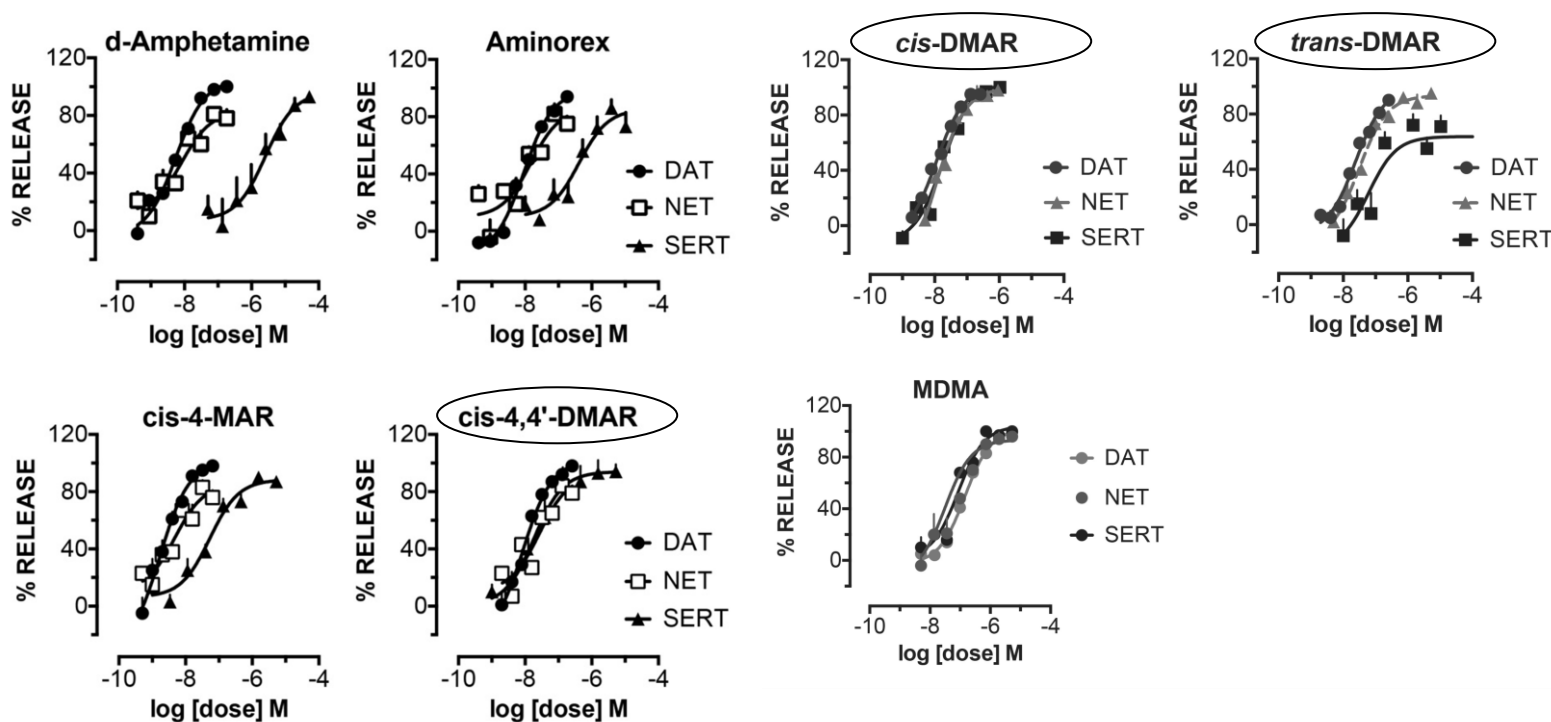
While a number of nonclinical studies have been published on the psychostimulant-like properties of 4-methylaminorex⁷⁻²¹ data on 4,4'-DMAR are more limited due to its recent emergence on the drug market.

Recent *in vitro* investigations on the monoamine transporter activity of cis-4,4'-DMAR using rat brain synaptosomes (based upon the methodology in^{22,23}) 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.¹ D-Amphetamine, aminorex and cis-4-MAR (4-methylaminorex) were used as control compounds. The determination of dose-response curves and potency values (expressed as half maximal effective concentrations, EC₅₀) 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 (EC₅₀ = 18.5 ± 2.8 nM). These results suggested that cis-4,4'-DMAR is a potent releaser at DAT, NET and SERT in rat brain tissue with comparable potency at DAT and NET to that of d-amphetamine and aminorex. The study also showed 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.¹

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 (refer to Figure and Table 1 below). 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.²⁴ (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.²⁵ The extent of the pharmacological overlaps between 4,4'-DMAR and MDMA observed in animals, may translate to humans. However, this has not been investigated.

Human data: There are no reported human clinical trials with 4,4'-DMAR.



Drug	Release at DAT EC ₅₀ (nM)	Release at NET EC ₅₀ (nM)	Release at SERT EC ₅₀ (nM)	DAT/SERT ratio
<i>d</i> -Amphetamine	5.5 ± 0.5	8.2 ± 1.6	2602 ± 494	473
Aminorex	9.1 ± 0.9	15.1 ± 3.5	414 ± 78	45
<i>cis</i> -4-MAR	1.7 ± 0.2	4.8 ± 0.9	53.2 ± 6.8	31
<i>cis</i> -4,4'-DMAR	8.6 ± 1.1	26.9 ± 5.9	18.5 ± 2.8	2
(S)-(+)-MDMA	143 ± 16	98.3 ± 15.0	85.0 ± 13.3	0.6
<i>cis</i> -4,4'-DMAR	10.9 ± 0.7	11.8 ± 2.0	17.7 ± 2.3	1.6
<i>trans</i> -4,4'-DMAR	24.4 ± 2.7	31.6 ± 4.6	59.9 ± 17.2	2.5

B. Routes of administration and dosage

As a powder or tablet, common routes of administration for 4,4'-DMAR are nasal insufflation and oral administration. 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. Reports of seizures and collected samples have noted that 4,4'-DMAR has typically been obtained in the form of powders and tablets.^{26,27} 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'. Some of the deaths reported from the United Kingdom involved "speckled" tablets featuring a 'Cherry' or 'cross' logo.⁵ The analysis of a collected sample of 5g 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.¹

One self-reported experience from a user website notes the inhalation of 20mg 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 40mg. In one of the deaths reported by Hungary the drug had been injected.²⁶

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. Another site reported the 'dosage' (not further described) as 30–100 mg. Oral 'doses' 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.

C. 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.²⁸ 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. 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. The trans-(4R,5R)-isomer differed significantly from the remaining isomers as it displayed high oral bioavailability and more than a 3-fold longer elimination half-life.¹⁶ Details on the potential for stereospecific pharmacokinetics related to 4,4'-DMAR have not been described.

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of 4,4'-DMAR.

Overall, there is insufficient clinical information to determine typical toxic effects of 4,4'-DMAR. However, the following symptoms have been reported in users: agitation, hyperthermia, hypertension, foaming at the mouth, breathing problems, convulsions, tachycardia and cardiac arrest.^{29,30,31} Although muscle rigidity and other symptoms that could be associated with a “serotonin syndrome” have been described in some fatalities, other drugs that capable of producing serotonergic effects (i.e. MDMA and mephedrone) were also detected (refer to Annex 1, Table 1). Therefore, the significance for 4,4'-DMAR is unclear.

6. Adverse reactions in humans

Non-fatal cases

One analytically confirmed non-fatal intoxication associated with 4,4'-DMAR has been reported in Poland. 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 bad, collapsed and vomited. On admission to hospital the patient was in general fair condition, with verbal contact, dilated pupils, blood pressure 110/70 and heart rate 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.

Fatal cases

A total of 32 analytically confirmed deaths associated with 4,4'-DMAR have been reported by Hungary (8 deaths), Poland (1 death) and the United Kingdom (23 deaths).^{26,33} 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 December 2014 (with the majority occurring in Northern Ireland in 2013). The final cause of death is not available for the majority of cases. Data on gender and age were available for 31 of the decedents. Twenty-three were males aged between 18 and 41 and eight were females aged between 16 and 43 years.

4,4'-DMAR was detected in post-mortem biological samples in all 32 deaths (see Annex 1; Table 1). 4,4'-DMAR was quantified in 27 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, the presence of one or more psychoactive substances and/or their metabolites was detected in post-mortem biological samples in addition to 4,4'-DMAR.

7. Dependence potential

See Section 8 (below)

8. Abuse potential

There are no published animal or human studies that have examined the dependence and abuse potential of 4,4'-DMAR. In addition, there are no published case reports describing the potential for dependence or abuse potential for 4,4'-DMAR. Information from drug treatment agencies about the dependence and abuse potential is not available. It was not possible to ascertain the dependence-producing properties nor abuse potential associated with 4,4'-DMAR from user websites.

In a review³³ based on the EMCDDA risk assessment report, they stated that although the low DAT/SERT ratio value in a stimulant is predictive of a mild capacity to induce reinforcing effects, pre-clinical evidence^{34,15} demonstrated that the 4,4'-DMAR related compound, 4-methylaminorex, produced rewarding properties via the dopamine system as well as amphetamine-like abuse liability. It was postulated that the potent dopamine-releasing activity of 4,4'-DMAR combined with the powerful psychostimulant effects may equally promote an addictive behavior.^{34.}

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

There are currently no therapeutic applications for 4,4'-DMAR. A range of 4,4'-DMAR isomers and closely related derivatives/analogues 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.^{35,36} The (4S,5S)-trans-4,4'-DMAR enantiomer has been featured in several patents related to the preparation of a range of phospholipase A2 inhibitors.³⁷ 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. There is no marketing authorisation (existing, ongoing or suspended) for 4,4'-DMAR.

10. Listing on the WHO Model List of Essential Medicines

4,4'-DMAR is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

4,4'-DMAR has never been marketed as a medicine.

12. Industrial use

4,4'-DMAR has no industrial use.

13. Non-medical use, abuse and dependence

4,4'-DMAR use and seized material was first reported in December 2012 in the Netherlands and the subsequently in Denmark, Finland, Hungary, Romania, Sweden, France and the United Kingdom.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

4,4'-DMAR use appears to be associated with the purchase of “research chemicals” or equivalent products via the Internet as well as “Ecstasy-like” tablets although it appears that the number of Internet shops advertising this particular substance may be declining. The use of tablets and powders in reported cases were associated with both home and recreational settings. Information obtained from user websites suggested that the intentional purchase of 4,4'-DMAR from Internet retailers may have been associated with ‘psychonauts’ who might have explored this substance in the home environment

(where an individual is on their own or in the company of others). Where information was available with regards to the reported death cases, it was reported that the users did not intentionally purchase 4,4'-DMAR on the street market but rather “Ecstasy” tablets or powders associated with other stimulant drugs.

Instances of misuse, abuse and dependence would be limited to individual users rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs. This was particularly evident in the fatalities where various drugs with the potential for toxic interactions (e.g. cathinones, phenethylamines, etc) were also involved. However, in some deaths involving no other drugs or those that may not produce catecholamine toxicity, 4,4'-DMAR would be considered to be contributory to the cause of death.

There are no specific prevalence data on the use of 4,4'-DMAR but available evidence does not suggest wide use of the substance.

15. Licit production, consumption and international trade

Not applicable.

16. Illicit manufacture and traffic and related information

No specific data.

17. Current international controls and their impact

None. Not applicable in relation to affecting impact of medical use.

18. Current and past national controls

4,4'-DMAR has recently been controlled in the United Kingdom, Germany, Slovenia and Sweden. In December 2014, a European Commission proposal for control in European Member States was made.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

None.

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Annex 1: Table 1. Deaths in which 4,4'-DMAR has been detected

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

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 Pentdrone 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 Pentdrone 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, died 12 hours later in hospital.
3	HU	June 2013	18	M	Blood ^u	+ (no quantitation)	Mephedrone (no quantitation) MDMA (no quantitation) Pentdrone (no	Myoclonus, unconsciousness, body temperature: 42.9°C, internal bleeding (oral,	Went out, did not go home. His parents found him on the street, in poor condition.

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
							quantitation)	intestinal), cardial and respiratorical arrest. Autopsy: large brain oedema, diffuse internal bleeding, bleeding in lungs, dilatation of the right ventricle and atrium.	Ambulance took him to the hospital, next morning died.
4	HU	Aug 2013	43	F	Blood ^f Urine	2.055 mg/L 5.928 mg/L	Mephedrone 0.5723 mg/L alpha-PVP 0.014 mg/L Alprazolam 0.1124 mg/L Mephedrone 0.3215 mg/L alpha-PVP 0.0056 mg/L Alprazolam 0.0534 mg/L OH-Alprazolam 0.027 mg/L	–	Found at home. No information on route of administration, however 'there was no pin- prick'.
5	HU	Sept 2013	20	F	Blood ^f Urine	3.565 mg/L 32.945 mg/L	Alprazolam 0.0951 mg/L alpha-PVP 0.0296 mg/L Pentredone 0.1730 mg/L THC-COOH 0.0127 mg/L Pentredone 44.544 mg/L Amphetamine 0.353 mg/L alpha-PVP 0.0844 mg/L Alprazolam 0.0167 mg/L	–	Died after a party. No information on route of administration, however 'there was no pin- prick'.

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.	Consumed drugs with her friend in the afternoon. Died 1 hour after admission to hospital.
7	HU	Oct 2013	27	M	Blood ^u	+ (no quantitation)	MDA 0.04 mg/L MDMA 0.8863 mg/L Mephedrone 0.0363 mg/L	Mild brain oedema, shock, in the heart right atrial and ventricular dilatation, intestinal bleeding.	Consumed drugs with his friends at 18:30, died next morning.
					Urine	+ (no quantitation)	MDA (no quantitation) MDMA (no quantitation) Mephedrone (no quantitation)		
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	<i>N</i> -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,	Found unconscious. Had seizures. A number of empty packages were found with the following labels: NEB, 3,4 DMMC, pentedrone, MDAI, 5-APB,

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
								spasm of the jaw muscles, bruising around lips and ears, BP 70/30 and pulse 140. Patient was intubated and gastric lavage was performed. Patient died of cardiac arrest. Resuscitation was ineffective.	bufedrone, Eth-Cat, MDEC, 3-MMC, IGNITE, 4-FMA, MXE, ethylphenidate, alpha-PVP and 4,4 DMAR.
10	UK	Jun 2013	36	M	Blood ^f	0.66 mg/L	Benzoylcoagnine 0.97 mg/L Cocaine <0.05 mg/L Codeine <0.02 mg/L 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 'methadone', 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	Benzoylcoagnine 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

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
									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	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.
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 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.

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
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	Methylone 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	~0.85 mg/L	Mephedrone ~0.045 mg/L	–	Collapsed at a party suspected over dose, taken to hospital unconscious and later died. Witnesses described her 'consuming ecstasy and snorting 'meth'.

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
					Blood ^u (ante mortem)	1.8 mg/L	Mephedrone <0.01 mg/L 4-MEC <0.01 mg/L Methylone <0.01 mg/L		
19	UK	Aug 2013	20	M	Blood ^f	1.6 mg/L	4-MEC 1.68 mg/L Methylone 0.26 mg/L 4-MMC (low level) Diazepam (low level) THC-COOH Indications of 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, methylone, 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 mephedrone detected on nasal swabs taken post-mortem.
20	UK	Sep 2013	21	M	Blood ^f	0.21 mg/L	Mephedrone 0.02 mg/L 4-MEC 0.1 mg/L Methylone 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, 'methadone' had been consumed. Taken to hospital

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
									(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.
21	UK	Sep 2013	31	M	Blood ^f	1.72 mg/L	Benzoyllecognine 0.55 mg/L Indications of low levels of cocaine and nordiazepam	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.

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
22	UK	Nov 2013	21	M	Blood ^f	1.75 mg/L	Methylone 0.14 mg/L 4-MEC 0.06 mg/L Mephedrone 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 tablets. 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 whilst out with friends.
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) Methylone 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 Ethanol 53 mg/dL	–	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. Severe heart disease at post mortem.	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

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
									quantity of drugs were allegedly available 'cocaine, speckled Rolex ecstasy tablets, magic and cannabis' and alcohol.
28	UK	Feb 2014	35	M	Blood ^f	3.5 mg/L	Methylone 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 Nordiazepam 0.09 mg/L THC-COOH	Fitting, unconscious and breathing.	Taking ecstasy tablets and legal highs, 'taking cocaine and ecstasy' 'fitting, unconscious and breathing' but died shortly after ambulance arrived.
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 (38.9°C)	Deceased believed she had taken 'MCAT' (mephedrone).
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" (usually mephedrone)

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
31	UK	June 2014	27	M	Blood ^f	18.68 mg/L	Mephedrone 15.73 mg/L (high) Cocaine 0.46 mg/L Benzoylecognine >2mg/L (high) Levamisole (low conc.) Hydroxyzine (low conc.)	Reported to be twitchy and sweating. Significant body rigidity was observed.	Collapsed and believed to have taken cocaine.
32	UK	Nov 2014	22	M	Blood ^f	4.13 mg/L	Mephedrone 2.17 mg/L MDMA Methoxphenidine Quinine Propranolol Mirtazapine metab Sertraline metab (all low concns)	Suffered cardiac arrest having taken various drugs	None