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EMCDDA-Europol Joint Report on a new psychoactive substance: 4-methylamphetamine

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

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1. Introduction

Article 5.1 of Council Decision 2005/387/JHA ⁽¹⁾ (hereinafter referred to as the 'Decision') stipulates that 'Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report (hereinafter the 'Joint Report').' The Joint Report shall be submitted to the Council, the European Medicines Agency (EMA) ⁽²⁾ and the Commission.

At the end of 2011 and in 2012, the EMCDDA and Europol examined the available information on a new psychoactive substance, 4-methylamphetamine, through a joint assessment based upon the following criteria:

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

The EMCDDA and Europol agreed that the information collected on 4-methylamphetamine satisfied all criteria (1 to 6). The two organisations therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on 4-methylamphetamine as stipulated by Article 5.1 of the Decision.

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

⁽²⁾ Formerly referred to as the EMEA.

2. Information collection process

In compliance with the provisions of the Decision, on 21 May 2012 the EMCDDA and Europol launched a procedure for the collection of information on 4-methylamphetamine, in order to prepare the Joint Report. The information was collected mainly through the respective networks in the Member States — Reitox national focal points (NFPs) and Europol national units (ENUs). In addition, the EMA collected information through the Member States' national competent authorities (NCAs) responsible for medicinal products. The information collection process was largely concluded by 2 July 2012; however, additional information and clarifications from some Member States were received up to four weeks after this date.

Europol asked the ENUs to provide information on:

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

Europol received responses from 23 Member States and Croatia.

According to Article 5.3 of the Decision, the EMA asked the Member States' national authorities responsible for human and veterinary medicinal products to provide information on whether:

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

Twenty Member States, Iceland and Norway replied to the EMA's request regarding human and/or veterinary medicinal products.

Furthermore, in anticipation of Article 7.3 of the Decision in relation to the manufacturing of medicinal products in the European Union, the EMCDDA and EMA also requested whether the new psychoactive substance 4-methylamphetamine is used to manufacture a medicinal product:

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

The rest of the information included in the Joint Report was collected by the EMCDDA through a structured questionnaire from the Reitox NFPs. The EMCDDA received replies from all 27 Member States as well as Croatia, Norway and Turkey.

A specific information request on whether or not 4-methylamphetamine is under assessment by the United Nations system was also made to the World Health Organization (see section 3.5). Furthermore, a literature review and structured Internet searches were carried out by the EMCDDA (see section 3.8.2). To facilitate the reading of the report, the full references of the quoted scientific articles are usually not included in the text; however, a list of the main information sources is annexed (Annex 1).

Thus, information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (partly). The information included in sections 3.4.1 (partly), 3.8.3 (partly), 4.1, 4.2 and 4.3 was provided by the EMA. The summary findings and the conclusion of the Joint Report were prepared and agreed by the two organisations responsible — the EMCDDA and Europol. A full account of the available images from both seizures and collected samples (Annex 2), and details on 4-methylamphetamine related fatalities (Annex 3) are also provided.

3. Information required by Article 5.2 of the Decision

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

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

Chemical description and names

4-Methylamphetamine is a ring-methylated derivative of amphetamine and belongs to the group of synthetic phenethylamines. In the 1950s, it was studied as an anorectic medicine by Smith, Kline & French laboratories (trade name: Aptrol⁽³⁾, see also section 3.8.3).

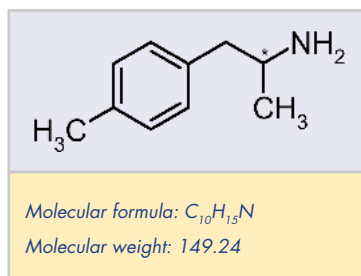
The systematic IUPAC name of 4-methylamphetamine is 1-(4-methylphenyl)propan-2-amine. Other chemical names encountered in the literature include 1-(4-methylphenyl)-2-aminopropane; 2-amino-1-(4-methylphenyl)propane or 2-amino-1-(*p*-methylphenyl)-propane; 1-(4-methylphenyl)-2-propylamine; α ,4-dimethylbenzeneethanamine (Chemical Abstract name); 1-(4-methylphenyl)-1-methylethanamine; *p*, α -dimethylphenethylamine; 4-methyl- α -methylphenethylamine; *para*-methylamphetamine or *p*-methylamphetamine; 1-methyl-2-*p*-tolyl-ethylamine; 1-(*p*-tolyl)-2-aminopropane; 1-(*p*-tolyl)propan-2-amine; 4-methylphenylisopropylamine; 1-methyl-2-*p*-tolyl-aethylamin; 2-amino-1-*p*-tolyl-propan; and, β -*p*-toluylisopropylamine.

4-Methylamphetamine is also known by some of its codenames – pTAP (from *para*-tolylaminopropane), PAL-313, 4-MeA or PmeA. 4-MA is extensively used as an abbreviation for 4-methylamphetamine; however, it is worth noting that the same abbreviation has also been used for *para*-methoxyamphetamine (also known as PMA). 4-Methylamphetamine should also not be confused with methamphetamine ('meth') or N-methylamphetamine, which is occasionally referred to in short as 'methylamphetamine'.

Positional isomers of 4-methylamphetamine are 2-methylamphetamine (also known as 'ortetamine'), and 3-methylamphetamine. The 4-ethyl and ring-dimethylated derivatives as well as the *N*-methyl isomer of 4-methylamphetamine (methamphetamine) are also known.

⁽³⁾ The trade name 'Aptrol' originally referred to the sulfate salt comprised of two moles of 4-MA and one mole of sulfuric acid with a molecular weight of 396.56.

The molecular structure, formula and weight of 4-methylamphetamine are shown below (asterisk indicates chiral centre).



Identification and analytical profile

Chemical Abstract Service (CAS) Registry Numbers: 64-11-9 (unspecified amine); 22683-78-9 (\pm amine); 41632-56-8 (hydrochloride salt); 50650-74-3 (sulfate as in 'Aptrol'); 788775-45-1 ((*R*)-(-) isomer).

Colour screening test: Marquis reagent – red; Mecke reagent – yellow; Mandelin reagent – brown.

Analysis using gas chromatography (GC) coupled with mass spectrometry (MS) is straightforward. Though the 2-, 3- and 4-isomers have virtually identical MS spectra, they can be distinguished based on their GC retention time. The infrared and nuclear magnetic resonance spectra of these positional isomers also differ.

Mass spectral data for 4-methylamphetamine (m/z): 44 (Electron Ionisation / EI spectrum base peak), 148 (M^+ , weak); 133 (Chemical Ionisation / CI spectrum base peak).

Immunoassay field tests for amphetamines are likely to give a positive reaction with 4-methylamphetamine.

Physical description

The free base of 4-methylamphetamine can be distilled in vacuum to provide a nearly colourless liquid ⁽⁴⁾ with an amine-like odour. Its water-soluble hydrochloride or sulfate salts are white or lightly coloured crystals.

Powders encountered containing 4-methylamphetamine also typically contained amphetamine and caffeine in varying ratios. Tablets and aqueous solutions ⁽⁵⁾ of the drug have also been seized.

⁽⁴⁾ A single paper (Jacobsen *et al.*, 1938) gives a melting point of '90–91' for the substance they prepared, however it is unclear whether this refers to the amine or its oxime precursor.

⁽⁵⁾ Germany reported a seizure of a nasal spray that contained a colourless, clear liquid also containing amphetamine and caffeine. As the hydrochloride salt is readily water-soluble it is possible that this was home-made from the powdery material.

No data are available on the enantiomeric composition of 4-methylamphetamine found in seizures, collected samples or biological samples ⁽⁶⁾.

Analytical reports of seized 4-methylamphetamine have not indicated the presence of other positional isomers.

Reference samples of high purity are commercially available ⁽⁷⁾.

A more detailed description of 4-methylamphetamine seizures encountered in the European Union Member States can be found in subsections 3.2.1 and 3.2.2 below.

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

4-Methylamphetamine appears to have been detected on a small number of occasions on the illicit drug market in Canada and the United States of America in the early 1970s. In Europe, a clinical case reporting the adverse effects of the use of 4-methylamphetamine sold as amphetamine in the United Kingdom dates back from 1989.

3.2.1 Information provided to Europol

The level of production, distribution and trafficking

The Netherlands reported that in recent years multiple illicit production sites and/or incidents related to the production of 4-methylamphetamine have been discovered. For example in 2010, production of 4-methylamphetamine was detected in three illicit amphetamine production laboratories. While in August 2011 traces of 4-methylamphetamine were found at amphetamine crystallisation site. However it is unclear whether those involved in the production were aware that they were producing 4-methylamphetamine. According to Dutch intelligence, there are indications that some producers believe that they were attempting to produce amphetamine using the precursor BMK, when they were actually using the precursor 4-methyl-BMK and subsequently producing 4-methylamphetamine (see section 3.8.1 for more information on precursors).

Other countries did not report any illicit or licit ⁽⁸⁾ production of 4-methylamphetamine to Europol.

⁽⁶⁾ Biological studies published including toxicological studies have used the racemic mixture – it is not known whether there are differences between the pharmacology and activity of the enantiomers of 4-methylamphetamine.

⁽⁷⁾ An example of a supplier of pure 4-methylamphetamine for use as a reference standard is LGC Standards, https://www.lgcstandards.com/epages/LGC.sf/en_GB/?ObjectPath=/Shops/LGC/Products/NMIAD895

⁽⁸⁾ See section 3.7 for information on control measures in the Member States.

Two Member States (Germany and France) reported seizures which clearly indicate that 4-methylamphetamine originated from the Netherlands.

Seven Member States reported seizures of 4-methylamphetamine as follows: Austria, Denmark, Finland, France, Germany, the Netherlands and Sweden. Croatia also reported seizures. Overall these ranged from a single seizure (Denmark, 1 gram) to several or dozens (France, Croatia, Sweden and Germany). In a significant majority of cases, 4-methylamphetamine was seized as mixture. The most common mixture was amphetamine, caffeine and 4-methylamphetamine (Croatia, Finland, France and Germany). The majority of these seizures were also reported to the EMCDDA (see section 3.2.2).

German authorities also reported seizures of the following mixtures:

- amphetamine, 4-methylamphetamine and para-methoxyamphetamine (PMA);
- 4-methylamphetamine and amphetamine;
- amphetamine, di(β -phenylisopropyl)amine (DPIA), 4-methylamphetamine and caffeine; and,
- 3,4-methylenedioxy-N-methylamphetamine (MDMA), amphetamine, 4-methylamphetamine, PMA and caffeine.

Only in a few cases (Germany and Sweden) was 4-methylamphetamine seized either as the main active substance in a mixture or as single compound. 4-Methylamphetamine was predominately seized as a powder and paste. However a few seizures reported to Europol noted that 4-methylamphetamine was seized as a liquid (France, Germany and Sweden).

The amount of drugs in individual cases, where 4-methylamphetamine was identified either in a mixture or as single compound, ranged from 0.02 g in Germany in 2011 to 147 kg seized in France in 2012. For example, Sweden reported that of 604 incidents where 4-methylamphetamine was identified, 36 kg of drugs were seized in powder form and 375 ml as liquids. For comparison, 4-methylamphetamine was detected in three cases reported by France where 237 kg of drugs were seized.

The bulk of amphetamine produced in the Netherlands is destined for export to other European countries (e.g. Spain, Scandinavian countries, United Kingdom, and Germany). As 4-methylamphetamine has been commonly found in mixtures with amphetamine, as well as detected at illicit amphetamine production laboratories, it is likely that 4-methylamphetamine is being exported to these countries as well. Indeed, the following significant seizures reported by France and Germany have indicated that 4-methylamphetamine has been sourced from the Netherlands:

- 9 kg of yellow liquid was seized in 2011. Analysis confirmed that it was mixture of 4-methylamphetamine and amphetamine. The drugs were transported from the Netherlands via France to United Kingdom.
- 10 kg of white powder was seized in 2011. Analysis confirmed that it was mixture of amphetamine, 4-methylamphetamine and caffeine. In addition, traces of the precursor 4-methyl-

BMK were found. The drugs were seized in rental car as it crossed the border from the Netherlands to Germany. Intelligence in this case suggested that the individual who was arrested had also smuggled a few shipments of amphetamine to Germany and Spain in the previous month.

- 81.7 kg of a white paste was seized in 2011. Analysis confirmed a mixture of 4-methylamphetamine, amphetamine and caffeine (19 %). The drugs were seized in transit to Spain.
- 2.2 kg of a powder was seized in 2012 in Kleve. Analysis confirmed that it contained amphetamine, PMA and traces of 4-methylamphetamine. The seizure took place as the courier was on his way from the Netherlands to Germany.
- 147 kg of a paste was seized in 2012. Analysis confirmed the presence of 4-methylamphetamine, caffeine and amphetamine. The drugs were seized in the area of Lille, which may suggest that it was in transit to the UK. To date this is the largest seizure concerning 4-methylamphetamine that has been reported to Europol.

Two countries (Italy and Germany) highlighted easy access to and availability of 4-methylamphetamine via Internet. Germany emphasised that smaller amounts of 4-methylamphetamine can be easily obtained via Internet shops situated in and out of the EU. Alongside this, larger amounts are sold via Internet trade boards, such as balticnordic.com or tradekey.com, predominantly from wholesalers (suppliers) in China or other Asian countries (see section 3.8.2 for EMCDDA searches of these sites and google.com).

3.2.2 Information provided to the EMCDDA

Twelve Member States reported 4-methylamphetamine detections ⁽⁹⁾ as follows: Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Luxembourg, the Netherlands, Poland, Sweden and the United Kingdom ⁽¹⁰⁾. Croatia and Norway also reported detections.

The seizures and collected samples referred to various physical forms, mostly powders of different colours (white, off-white, yellow, and to a lesser extent beige, brown and pink) found in all the countries that reported detections; as a paste (white, yellow) in Austria, Belgium, France and the United Kingdom; a liquid in France and Sweden; and a small number of tablets in the Netherlands. Norway reported a seizure of tablets containing 4-methylamphetamine in a product marketed as a weight-loss supplement (for more details see *Seizures*, below). Germany reported a seizure of a nasal spray containing 4-methylamphetamine, amphetamine and caffeine ⁽⁵⁾.

⁽⁹⁾ 'Detections' is an all encompassing term, which 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.)

⁽¹⁰⁾ The Bulgarian NFP reported that earlier in 2012 the analysis of one sample (a mixture of different substances, seized by the Police and sent to National Institute of Criminology for analysis) raised suspicions that one of the substances present could be 4-methylamphetamine although this has not been confirmed.

Seizures

In most cases 4-methylamphetamine was seized as a mixture, the most common of which was amphetamine, 4-methylamphetamine and caffeine. In most cases the amount of 4-methylamphetamine present was not reported. In other cases, the amount reported ranged from being a trace or minor component to a smaller number of reports where 4-methylamphetamine was a larger or main component of the mixture. In a small number of seizures 4-methylamphetamine was the only active substance detected (reported by Belgium, Denmark, France, Germany, Luxembourg, the Netherlands and Sweden) ^(11, 12).

Three Member States and Norway reported small seizures, which varied from single seizures in Denmark (1 g; personal use) and Luxembourg (6 g), three seizures in Norway (0.345, 0.136 g and 120 tablets) and four in Poland (2 g each). The 120 tablets reported by Norway had been seized by customs at Oslo in December 2009. They were found in a product labelled 'Green Stinger' which is marketed in the United States and on the Internet as a weight loss supplement. According to the product label it contained 'Ephedra extract' among other ingredients. Analysis revealed that no ephedrine was present. However the analytical data indicated a mix of several compounds: 1-phenylethylamine, 2-phenylethylamine, β -methyl-phenethylamine, N,N-dimethyl-phenethylamine, 4-methylamphetamine, N-benzyl-1-phenylethylamine, yohimbine and caffeine.

Croatia reported 28 seizures totalling 519.8 g where 4-methylamphetamine was found in trace amounts in amphetamine samples (first reported to the EMCDDA in 2010). Belgium reported three seizures: in October 2009, approximately 500 g of a paste was seized that only contained 4-methylamphetamine as an active substance. This was the first official EMCDDA–Europol notification of 4-methylamphetamine (see section 3.6). In May 2012, a yellow-white powder was seized that contained amphetamine sulphate (23 %) and 4-methylamphetamine hydrochloride salt (37 %). Also in May 2012, a seizure of 82 grams of a yellow paste containing amphetamine sulphate (13 %), 4-methylamphetamine hydrochloride salt (21 %) and caffeine (16 %) was made. Finland reported that all seizures from 2011 that contained 4-methylamphetamine also contained amphetamine ⁽¹³⁾. No samples containing 4-methylamphetamine have been detected in 2012.

The first seizure in Sweden was in December 2009 where 7.28 g of a yellow powder was found to contain 4-methylamphetamine only. In 2010 there were 198 cases, while in 2011 there were 256 cases and 17 liquid samples where 4-methylamphetamine was detected in mixtures that contained controlled drugs (such as amphetamine). In 2012 there have been a further 57 seizures. In approximately 90 % of all these cases, 4-methylamphetamine was either in a mixture with amphetamine or amphetamine with caffeine. The weight of seizures ranged from 1 g to 2 kg. In the remaining 10 % of cases, 4-methylamphetamine was found together with caffeine and weighed between 0.5 g to 1 kg. In a few cases 4-methylamphetamine was the only active substance detected. There were also a few cases where 4-methylamphetamine was detected with metamphetamine.

⁽¹¹⁾ France reported a seizure of an unknown date and an unknown quantity of a yellow powder containing 4-methylamphetamine. It is unknown if any other substances were detected.

⁽¹²⁾ Some of these also contained caffeine.

⁽¹³⁾ The 2011 Final EWS Report to the EMCDDA from Finland notes a total of 1070 g seized in 32 police cases.

Hungary reported seizures of just over 1.8 kg of powder, most of which contained 2–3 % amphetamine with a similar concentration of 4-methylamphetamine. Austria reported five seizures of a yellow powder totalling 2.3 kg which in each case also contained amphetamine.

The Netherlands reported that there had been 1560 amphetamine samples (powders) analysed in 2011 ⁽¹⁴⁾. Of these, 81 samples contained amphetamine in combination with 4-methylamphetamine; 27 samples contained 4-methylamphetamine only; and, 37 samples contained minimal amounts of 4-methylamphetamine. A further 461 amphetamine samples (powders) have been analysed in 2012. Of these, 30 samples contained amphetamine in combination with a substantial amount of 4-methylamphetamine; 11 samples contained 4-methylamphetamine only; and, 44 samples contained minimal amounts of 4-methylamphetamine. Overall these seizures were mostly from production locations.

Germany reported 57 seizures where 4-methylamphetamine has been detected (the first was in March 2010). These ranged from trace amounts found in amphetamine samples, to seizures that contained greater amounts of 4-methylamphetamine. This includes four seizures where amphetamine and 4-methylamphetamine were present in equal amounts, and a few samples where 4-methylamphetamine was the main component in a mixture with amphetamine and caffeine. A few seizures were reported where 4-methylamphetamine was detected as the only active substance (e.g. 744.5 g seized in July 2010) ⁽¹⁵⁾. One such seizure included three plastic bags, one of which was labelled '2,0 g PEP' ⁽¹⁶⁾ and two others labelled '1,2 G PEP' the contents of which only contained 4-methylamphetamine and caffeine.

The United Kingdom reported 15 seizures totalling approximately 35 kg (the first seizure was in May 2010). In each case amphetamine was also detected. Most were small seizures of white/off-white powders; one seizure was of 967 g ⁽¹⁷⁾; another seizure of approximately 34 kg in April 2012 contained 14 % amphetamine and although the concentration of 4-methylamphetamine was not determined it was known to be lower than the amphetamine present.

France reported five seizures ⁽¹⁸⁾ totalling approximately 280 kg: one seizure of 9 kg of a liquid (see below) which also contained amphetamine. Three seizures of paste weighing 81.7 kg (see below), 147 kg and 42 kg respectively were also made. All three also contained amphetamine and caffeine.

Indications of international trafficking were reported by two Member States ⁽¹⁹⁾ (see section 3.2.1 for more details). In 2011 French authorities seized 9 kg of a liquid containing

⁽¹⁴⁾ The 2011 Final EWS Report to the EMCDDA from the Netherlands notes a total of 6.3 kg seized.

⁽¹⁵⁾ In most of these cases caffeine was also detected.

⁽¹⁶⁾ 'Pep' is a street name for amphetamine.

⁽¹⁷⁾ The largest peak on the chromatograph was amphetamine. It also contained caffeine.

⁽¹⁸⁾ One of these seizures was of an unknown date and an unknown quantity of a yellow powder containing 4-methylamphetamine.

⁽¹⁹⁾ On 17 October 2011 the Polish NFP reported a seizure in October 2011 of four samples of powder that weighed 2 g each (two samples were light yellow in colour, two were light pink), total weight of seizure unknown. The samples contained 83–86 % amphetamine sulphate, a small amount of 4-methylamphetamine and di-(β-phenylisopropyl)-amine. Context: international trafficking; scale of trafficking unknown.

4-methylamphetamine and amphetamine while in transit from the Netherlands to the United Kingdom; while 81.7 kg of a white paste containing 4-methylamphetamine, amphetamine (19 %) and caffeine was seized in transit from the Netherlands to Spain. In May 2011 German authorities seized 10 kg of a white powder containing 4-methylamphetamine, amphetamine, caffeine and traces of 4-methyl-BMK from a courier in a rental car that had crossed the border from the Netherlands. According to witness statements the courier had trafficked several kilograms of amphetamine to Germany and Spain during the previous month. In February 2012 authorities seized 2.2 kg of drugs from a courier travelling from the Netherlands to Germany. The sample contained amphetamine, 4-methoxyamphetamine and a smaller amount of 4-methylamphetamine.

Biological samples

Six Member States reported biological detections of 4-methylamphetamine as follows: Belgium, Denmark, Hungary, the Netherlands, Sweden, and the United Kingdom (see section 3.4.1 and Annex 3 for more details).

The lack of a rapid qualitative screening method is a limiting factor for the detection of 4-methylamphetamine in biological samples. Furthermore, many European forensic/toxicological laboratories might not have a procedure in place for analysing 4-methylamphetamine in biological samples. This may be due to the lack of reference standards for the drug in some laboratories or, especially, for its metabolites.

Belgium reported six samples where 4-methylamphetamine was detected either in post-mortem blood, urine or tissues (obtained between August 2011 and July 2012), one sample where it was detected in ante-mortem blood (2011), and one sample where it was detected in ante-mortem urine (2011).

Denmark reported one sample (obtained in December 2010) where 4-methylamphetamine or other isomers were detected post-mortem.

The Netherlands reported six samples (four samples were obtained in 2011; two in 2012) where 4-methylamphetamine was detected in post-mortem blood.

The United Kingdom reported three samples (obtained between October 2010 and January 2012) where 4-methylamphetamine was detected in post-mortem blood. Furthermore, two additional samples from a suspected 4-methylamphetamine related fatality and a non-fatal intoxication were obtained in April 2012; the results of the analyses are not yet available.

Sweden reported the detection of 4-methylamphetamine in ante-mortem urine samples in six cases (obtained between April 2011 and March 2012). In all cases amphetamine was also detected. Further, the Swedish project STRIDA, that analyses urine and serum samples in drug exposed patients, detected 4-methylamphetamine in the urine of four non-fatal intoxications at two different hospitals in May 2012.

Hungary reported the detection of 4-methylamphetamine in two ante-mortem urine samples (obtained in 2012). In both cases amphetamine was also detected. The samples were provided by the police from persons who were tested due to drug-related offences.

Collected samples, availability and content of 4-methylamphetamine products

In addition to the detections of 4-methylamphetamine in seizures and biological samples, four Member States (Austria, Belgium, France and the Netherlands) also reported collected samples.

In the Netherlands, the Drugs Information and Monitoring System (DIMS) first detected 4-methylamphetamine in collected 'speed' ⁽²⁰⁾ samples in 2009. 1006 'speed' samples (powders) were analysed in 2010, of these 10 % contained 4-methylamphetamine. 946 'speed' samples (powders) were analysed 2011, of these 9 % contained 4-methylamphetamine. 685 'speed' samples were analysed in 2012, of these 17 % contained 4-methylamphetamine. Six tablets were also analysed in 2012 and found to contain both amphetamine and 4-methylamphetamine.

In October of 2010, the French Monitoring Centre for Drugs and Drug Addiction (OFDT) reported a non-fatal intoxication linked to the use of 4-methylamphetamine. Analysis of the collected sample found it to be a mixture of amphetamine (10 %) and 4-methylamphetamine (see section 3.4.1).

Belgium reported five collected samples of powders between August 2011 and March 2012 as part of investigations into four fatalities and a non-fatal intoxication linked to the use of 'speed' that contained 4-methylamphetamine and amphetamine. In three cases (two fatalities and a non-fatal intoxication) where the substances were quantified, the concentration of 4-methylamphetamine was greater than amphetamine (see section 3.4.1 and Annex 3).

In April and May 2012 in Austria, six samples of white powders ⁽²¹⁾, weighing between 0.060 and 1.126 g, were collected from two different parties and analysed as part of the 'pill'-testing project run by 'ChEckiT!'. In all the cases the samples were sold as 'speed'. The price paid was available for four samples and ranged between 15 and 30 €/g. All six samples contained amphetamine as the main active substance (34–208 mg/g). 4-Methylamphetamine was also detected (4–24 mg/g). All the samples contained caffeine. Other substances found in some of the samples included paracetamol, ephedrine, and 4-methylethcathinone (4-MEC).

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

The available evidence suggests that in many cases 4-methylamphetamine is produced and trafficked by the same organised crime groups that are involved with the production and trafficking of amphetamine.

According to information provided to Europol from the Netherlands no distinct difference can be made between 4-methylamphetamine and amphetamine in terms of the involvement of organised

⁽²⁰⁾ 'Speed' is a common 'street' name used for amphetamine. Other names include 'wizz', 'whizz', and 'base'.

⁽²¹⁾ One sample was reported as a 'crumbly' white powder; another sample was reported as 'paste-like'.

crime groups, production, trade, and/or users. It is assumed that aspects such as violence and/or money laundering can not be specifically attributed to the production and trade of 4-methylamphetamine. Rather they are elements of a broader context of organised (synthetic) drugs crime, in which money laundering and violence are part of the criminal business process.

Based on the information provided to Europol by the Member States, it is difficult to determine if the organised criminal groups responsible for the illicit manufacture and trafficking of amphetamine are intentionally producing 4-methylamphetamine. According to intelligence from Dutch police it appears that in a few cases the producers believed that they were synthesising amphetamine using the precursor benzyl methyl ketone (BMK; phenylacetone). It is unknown if organised crime groups involved in the shipment of precursors used in the production of amphetamine have deliberately or inadvertently supplied 4-methyl-BMK instead of BMK (see section 3.8.1).

Money laundering aspects

No information was received on money laundering related to the production and/or trafficking of 4-methylamphetamine.

Violence in connection with production, wholesale and distribution

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

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

3.4.1 First indication of health risks

4-methylamphetamine related deaths

Four Member States (Belgium, Denmark, the Netherlands, and the United Kingdom) reported a total of sixteen deaths where 4-methylamphetamine was detected in post-mortem samples (see *Biological samples* in section 3.2.2 and Annex 3 for further details). The first death was in the United Kingdom in October 2010.

Belgium reported six deaths (occurring between August 2011 and July 2012) where 4-methylamphetamine was detected either in post-mortem blood, urine or tissues. In all cases amphetamine was also detected. Due to concerns over the number of 4-methylamphetamine related deaths in Belgium, a risk assessment at national level was conducted in May 2012. Here it is noted that in all the reported deaths (five at the time of the risk assessment), as well non-fatal intoxications,

the individuals had consumed a powder sold as 'speed' and were recreational drug users. In four of the deaths, a sample of powder collected during the course of the investigations was analysed and found to contain 4-methylamphetamine, amphetamine and caffeine. In two of these samples the active substances were quantified and 4-methylamphetamine was present in greater amounts than amphetamine (and caffeine).

Denmark reported one death (December 2010) where 4-methylamphetamine or its isomers were detected post-mortem. Amphetamine was also detected, among other substances.

The Netherlands reported six deaths (four in 2011 and two in 2012) where 4-methylamphetamine was detected in post-mortem blood. In all cases amphetamine was also detected.

The United Kingdom reported three deaths (between October 2010 and January 2012) where 4-methylamphetamine was detected in post-mortem blood. Amphetamine was detected in only one case.

Non-fatal intoxications

A total of nine non-fatal intoxications were reported by four Member States (Belgium, France, Sweden, and the United Kingdom). 4-Methylamphetamine was detected in biological samples (urine or blood) in six of these cases (Belgium and Sweden).

Belgium reported three non-fatal intoxications (two occurred in August 2011 and one in September 2011). In two cases, 4-methylamphetamine was detected in blood or urine. In the third case, analysis of a powder collected as part of the investigation was found to contain 4-methylamphetamine (64 %), amphetamine (16 %) and caffeine (15 %).

Sweden reported four non-fatal intoxications from urine samples collected in May 2012 from emergency wards at two hospitals as part of the STRIDA project (see section 3.2.2).

France reported a non-fatal intoxication (from June 2010). While the user thought that he was using amphetamine (in a white paste), analysis found it to be a mixture of amphetamine (10 %) and 4-methylamphetamine ⁽²²⁾. The user injected intravenously 1.5 grams of the paste over a twelve-hour period. Twenty four hours later, he was admitted into hospital with nausea, sweating, paranoia, hallucinations and symptoms of depression once the effects of the substance were gone. The user had also consumed alcohol, cannabis, Zyprexa 10 mg (olanzapine), Tégretol (carbamazepine) and methadone.

The United Kingdom reported a non-fatal intoxication (from April 2012). Toxicology results are not currently available. However, analysis of a substance seized as part of the investigation detected 4-methylamphetamine and amphetamine (< 1 %).

⁽²²⁾ No biological sample was available for analysis in this case.

Acute animal toxicity data

Acute animal toxicity data of 4-methylamphetamine as compared to amphetamine reported in the scientific literature, and expressed as median lethal dose (LD₅₀) and mg/kg units is listed below ⁽²³⁾:

- LD₅₀ = 136 mg/kg (ip, mouse) (for amphetamine, the comparative value is 101 mg/kg) (Marsh and Herring, 1950);
- LD₅₀ = 31.0 mg/kg (iv, mouse) (for amphetamine, the comparative value is 12.5 mg/kg), LD₅₀ = 115 mg/kg (oral, mouse) (for amphetamine, the comparative value is 45 mg/kg) (Haas and Forth, 1956);
- LD₅₀ = 12 mg/kg (ip, mouse) (for amphetamine, the comparative value is 40 mg/kg) (Benington *et al.*, 1965);
- LD₅₀ = 160 mg/kg (sc, mouse kept individually in isolation) (for amphetamine, the comparative value is 205 mg/kg), LD₅₀ = 35 mg/kg (sc, mouse kept in groups of ten) (for amphetamine, the comparative value is 15.5 mg/kg) (Riva *et al.*, 1969).

Information on toxicity, tolerance and dependence

There have been limited studies on the toxicity and potential for tolerance and dependence of 4-methylamphetamine.

The only available study that has investigated 4-methylamphetamine in humans was published in 1952 (see section 3.1 and 3.8.3). This was a clinical trial that examined the use of the substance as an anorectic agent. However, the limitations in the study design limit the relevance of this publication.

There is some evidence from *in vitro* and *in vivo* animal studies to suggest that elevating extracellular serotonin in the brain antagonises the stimulant properties of dopamine-releasing drugs such as amphetamine. One possible hypothesis discussed in the Belgian risk assessment is that *in vitro* and *in vivo* animal studies have found that administration of 4-methylamphetamine caused a greater release of serotonin in the brain compared to other amphetamine analogues that were evaluated. Although studies in humans are lacking, 4-methylamphetamine may dampen the desired stimulant effects of drugs such as amphetamine (which are mediated by dopamine). In order to compensate for a lack/or diminished stimulant effects this may lead to increased consumption/repeated (over-)dosing in users who believe that they are taking amphetamine. Depending on the composition of the drugs consumed, it could be possible that this could lead to combined symptoms of toxicity from noradrenaline, dopamine and serotonin (particularly given that 4-methylamphetamine is often found in mixtures with amphetamine). It may also be possible that given the reported effects on serotonin release from *in vitro* and *in vivo* animal studies, 4-methylamphetamine may induce a serotonin syndrome. However, given the lack of study of 4-methylamphetamine caution is required in extrapolating these data to humans.

⁽²³⁾ ip = intraperitoneal; iv = intravenous; sc = subcutaneous

There have been no studies investigating the potential for tolerance and dependence of 4-methylamphetamine in humans. Studies in animals have demonstrated that 4-methylamphetamine supports less self-administration behaviour when compared with 3-methylamphetamine, 4-fluoroamphetamine, and 3-fluoroamphetamine. While further study of this is required, one possible hypothesis is that 4-methylamphetamine demonstrates less abuse potential than the other substances studied.

Information from the EU pharmacovigilance system

The EMA reported that there had been no reports related to 4-methylamphetamine transmitted to Eudravigilance.

User reports

The available evidence suggests that in most cases 4-methylamphetamine is sold as amphetamine, and that users are usually unaware of this. Moreover, there appears to be little demand for 4-methylamphetamine. These reasons are likely to account for the limited number of user reports of 4-methylamphetamine on Internet drug discussion forums and other websites. Those reports that are available should be interpreted with caution ⁽²⁴⁾.

France reported some information collected from Internet forums where users have shared their using experiences of 4-methylamphetamine. The vast majority of effects reported by users are negative. Positive effects are rarely reported. Adverse effects include anxiety, immediately followed by a feeling of empathy and euphoria, with post-use effects such as insomnia, cognitive disorder, mood disorder that can be made durable in case of repeated use. Ephedra-type stimulant effects that are described by users as terrible, with both physical and psychological effects, including: substantial sweating, nausea, abdominal pains, high blood pressure, flutter, headache, paranoia, hallucinations, anxiety, depression. Administration of 4-methylamphetamine include ingestion, sniffing, inhalation and intramuscular injection. Doses administered may vary from 10-50 mg to 100-150 or 200-300 mg orally.

The above information should be viewed with caution as it does not result from a first hand account. Furthermore, as explained above, confusion between 4-methylamphetamine and *para*-methoxyamphetamine or methylamphetamine (methamphetamine) is possible.

3.4.2 Characteristics of users

Prevalence data on the use of 4-methylamphetamine are not available. The available evidence suggests that in a number of countries where 4-methylamphetamine has been detected it has been sold as amphetamine (typically as 'speed'). It can be generally assumed that recreational and

⁽²⁴⁾ See: <http://www.bluelight.ru/vb/threads/419580-4-methylamphetamine> and <http://www.drugs-forum.com/forum/tags.php?tag=4-methylamphetamine>

problematic users of amphetamines are at risk of exposure to 4-methylamphetamine. The patterns of use are also likely to be the same as amphetamine. 4-Methylamphetamine is likely to be ingested, snorted (nasal insufflation) or injected. There is no information on smoking ('free basing') 4-methylamphetamine ⁽²⁵⁾.

Information provided by Belgium, France, the Netherlands, Sweden, and the United Kingdom also note that there is little or no evidence to suggest specific demand for 4-methylamphetamine (see section 3.8.2).

Prevalence of amphetamine use

Drug prevalence estimates suggest that about 2 million Europeans have used amphetamines during the last year, with about 12.5 million using them at some stage of their lives ^(26,27). Among young adults (15–34 years), lifetime prevalence of amphetamines use varies considerably between countries, from 0.1 % to 14.3 %, with a weighted European average of 5.0 %. Last year use of amphetamines in this age group ranges from 0.1 % to 2.5 %, with most countries reporting prevalence levels of 0.5–2.0 %. It is estimated that about 1.5 million (1.1 %) young Europeans have used amphetamines during the last year.

Among 15- to 16-year-old school students, lifetime prevalence of amphetamines use ranged from 1 % to 8 % in the 26 EU Member States, Croatia and Norway, surveyed in 2007.

Data on the prevalence of amphetamines use in nightlife settings in 2009, provided by four countries (Belgium, Czech Republic, the Netherlands, and the United Kingdom), show considerable variation, ranging from 6 % to 24 % for last year use of amphetamines.

Over the last decade, last year amphetamines use has remained relatively low and stable in most European countries, with prevalence levels of less than 3 % for almost all reporting countries. In the United Kingdom, last year use of amphetamines among young adults (15–34) declined from 6.2 % in 1998 to 1.8 % in 2009–10; in Denmark, after increasing to 3.1 % in 2000, it declined to 2 % in 2010. During the period 2004–09, only Norway and the Czech Republic reported a change of more than one percentage point in last year prevalence of amphetamines use among young adults. In the Czech Republic, differences in survey methods do not allow confirmation of recent trends. School surveys suggest, overall, little change in the levels of experimentation with amphetamines among school students aged 15–16 years. Between 2003 and 2007, most countries reported both low and stable trends in lifetime prevalence in this group.

⁽²⁵⁾ The term 'free basing' refers to inhaling the volatiles (fumes) of the amine (the free base is liberated from the amine salt). For example, methamphetamine can be used in this way.

⁽²⁶⁾ As European estimates are based on surveys conducted between 2001 and 2009/10 (mainly 2004–08), they do not refer to a single year. The data summarised here are available under 'General population surveys' in the EMCDDA's 2011 statistical bulletin. See: <http://www.emcdda.europa.eu/stats11/gps>

⁽²⁷⁾ EMCDDA (2011), Annual report 2011: the state of the drugs problem in Europe, Publications Office of the European Union, Luxembourg.

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

The World Health Organization (WHO) is the specialised United Nations (UN) Agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the 1961 and 1971 UN Conventions. On 22 June 2012, WHO informed the EMCDDA that 4-methylamphetamine is currently not under assessment and has not been under assessment by the UN system.

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

The first official EMCDDA–Europol notification of 4-methylamphetamine dates from 14 December 2009 from the Belgian Reitox NFP. The reporting form details a seizure of 16 bags made in Flanders in October 2009 by the local police services. Each bag contained a piece of yellow paste in aluminium foil. Nine bags contained about 5 g of paste; one bag 39 g; and, six bags 70 to 80 g. 4-Methylphenylacetone was also detected.

4-Methylamphetamine was added to the list of new psychoactive substances monitored by the EMCDDA and Europol via the early warning system and a profile of the substance was created in the EMCDDA European database on new drugs (EDND). Analytical details and background information have been exchanged on various occasions between EMCDDA, Europol and the Member States. The Commission and the EMA were kept duly informed.

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

Six Member States (Cyprus, Denmark, Ireland, Lithuania, the Netherlands and the United Kingdom) as well as Croatia control 4-methylamphetamine under drug control or equivalent legislation. In Cyprus, Ireland, Lithuania and the United Kingdom 4-methylamphetamine is controlled using a generic definition of phenethylamines.

In Cyprus, 4-methylamphetamine is controlled under the Narcotic Drugs and Psychotropic Substances Law of 1977. In Denmark, 4-methylamphetamine and 2-methylamphetamine were added to the Danish lists of controlled substances in 2011. In Ireland, 4-methylamphetamine is controlled under the Misuse of Drugs Act, 1977. In Lithuania it is controlled by the generic definition of phenethylamines of May 2012. In the Netherlands, 4-methylamphetamine is controlled under Opium Law. In the United Kingdom, 4-methylamphetamine is controlled under the Misuse of

Drugs Act 1971. In Croatia, 4-methylamphetamine has been controlled under the List of Drugs, Psychotropic Substances, Plants Used to Produce Drugs and Substances that can be Used in the Production of Drugs.

Two Member States have legislation limiting unauthorised supply of defined or qualifying psychoactive substances. In Austria, 4-methylamphetamine is controlled under the Act on New Psychoactive Substances. In Hungary, 4-methylamphetamine is controlled as it is covered by the structural description of phenethylamines of schedule C of Government Decree 66/2012. Both Austria and Hungary control the substance within a generic definition of phenethylamines.

Two Member States (Germany and Finland) have controlled 4-methylamphetamine under their medicines legislation. In Germany in accordance with diverse articles of the Medical Products Act (Arzneimittelgesetz, AMG), trafficking of 4-methylamphetamine and keeping 4-methylamphetamine for sale are forbidden and may be punished. In Finland 4-methylamphetamine was classified as a medicine under the Medicines Act (395/1987).

Finally, it may be noted that laws were passed in Ireland (2010), Poland (2010) and Romania (2011), to penalise unauthorised supply of any psychoactive substance that qualifies by conforming to certain criteria, and national authorities may find that 4-methylamphetamine meets such criteria.

In 19 Member States, 4-methylamphetamine is not controlled under drug control laws. Belgium, Germany and Italy noted that they intend to introduce such controls although it is unknown when these measures will come into effect. In France, the National Narcotic and Psychotropic Substances Board proposed in April 2012 that 4-methylamphetamine should be classified as a narcotic drug. 4-Methylamphetamine is not controlled in Norway or Turkey.

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

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

The available information suggests that the precursor used for the manufacture of 4-methylamphetamine is 4-methyl-benzyl methyl ketone (4-methyl-BMK) ⁽²⁸⁾, which is not under international control. It can be potentially used in organic synthesis and appears to be commercially available. Websites were identified that sold 4-methyl-BMK. Quotations were requested for 1 or 10 kg of 4-methyl-BMK on lookchem.com or directly from advertisers found on the Internet. This resulted in several responses received by email from companies that appear to be based in China that detailed the price per kilogram, as well as information on payment, shipping, delivery and/or purity.

⁽²⁸⁾ Other chemical names are 4-methylphenylacetone and 1-(4-methylphenyl)propan-2-one.

In some of the seized samples, detectable amounts of 4-methyl-BMK and BMK ⁽²⁹⁾ have been found, suggesting that 4-methylamphetamine and amphetamine may have been synthesised in the same batch from the mixture of their respective precursors.

According to Dutch intelligence (see section 3.2.1), there are indications that some producers believe that they are attempting to produce amphetamine using the precursor BMK, when they are actually using 4-methyl-BMK and subsequently producing 4-methylamphetamine.

In Belgium and the Netherlands it has been hypothesised that the presence of 4-methylamphetamine in amphetamine ('speed') samples (see section 3.2.2) is probably due to a change in the precursors used for the illegal synthesis of amphetamine. Alternatively, it has also been suggested that a mixture of BMK and 4-methyl-BMK is being used by illicit labs that have imported the precursors from China/Russia for amphetamine synthesis ⁽³⁰⁾. Information on a sample analysed indicates that amphetamine and 4-methylamphetamine had been probably manufactured in the same batch (a mixed amine dimer was formed from phenylacetone and 4-phenylacetone indicative of the simultaneous presence in the reaction mixture).

The synthesis of 4-methylamphetamine requires similar equipment and chemical expertise to that needed for the production of amphetamines. Most employed methods to synthesise 4-methylamphetamine include reductive amination of the respective 4-methylphenylacetone and use of the Leuckart reaction. Both reactions are feasible in an amateur laboratory setting and do not require sophisticated equipment.

In the first reported synthesis of 4-methylamphetamine published in 1938 by Jacobsen *et al.* 'p-Toluylacetoxim' was reduced by sodium amalgam to obtain the title compound. An independent patent filed in the same year describes the synthesis of 4-methylamphetamine based on the Leuckart method (Nabenhauer, 1941). The key precursor in both procedures is 4-methylphenylacetone. Alternative syntheses, such as the one using *p*-tolualdehyde (4-methylbenzaldehyde) and nitroethane as starting materials (Knoevenagel Condensation) followed by reduction with lithium aluminium hydride (LiAlH₄) have also been described in the literature. Methods providing enantiomerically enriched 4-methylamphetamine are also known.

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

As noted, the available evidence suggests that in many cases 4-methylamphetamine is sold as amphetamine (typically as 'speed'). The mode and scope of use is therefore likely to resemble amphetamine use. There is little evidence to suggest specific demand for 4-methylamphetamine.

For example, Belgium and the Netherlands have reported that 4-methylamphetamine has been sold at the street-level as 'speed' and that there does not appear to be a specific demand for it. As such,

⁽²⁹⁾ BMK (benzyl methyl ketone), also known as phenylacetone or phenylpropan-2-one (P2P) is the main precursor used in the manufacture of amphetamine and methamphetamine.

⁽³⁰⁾ Risk assessment of 4-methylamphetamine in Belgium, 03/05/2012.

users are unlikely to be aware that they are consuming it. France and Sweden also reported that there appears to be little specific demand for 4-methylamphetamine. Belgium noted that 4-methylamphetamine is not sold as 'a new drug' or a 'legal high'. In the United Kingdom police seizures suggests that 4-methylamphetamine is mainly sold at the street-level.

An online search of Google by the United Kingdom did not find any websites selling 4-methylamphetamine. A search of Silk Road, an anonymous online marketplace that specialises in products that are illegal in many jurisdictions, did not find any 4-methylamphetamine being sold by sellers purporting to be from the United Kingdom. None of the countries reported seizures or collected samples linked to Internet sales.

Italy and Sweden noted that 4-methylamphetamine was sold as a 'research chemical' on the Internet. France reported that the availability of 4-methylamphetamine on the Internet appeared to be low. No information on price or websites were reported.

A structured search of balticnordic.com, tradekey.com and google.com using English search terms and based on the EMCDDA snapshot methodology⁽³¹⁾ was conducted by the EMCDDA at the time of writing this report⁽³²⁾. No sites were identified that sold 4-methylamphetamine aimed at consumers (i.e. as a 'legal high' or 'research chemical'). Websites were identified that sold 4-methylamphetamine as a fine chemical, such as for use as an analytical reference standard (see footnote 7) or for scientific research purposes⁽³³⁾. Furthermore, some websites/web portals listed chemical suppliers that could purportedly offer 4-methylamphetamine for sale.

Slovakia undertook a structured Internet search in June 2012 in Slovak on two search engines including Google Slovakia⁽³⁴⁾. No websites selling or advertising 4-methylamphetamine were identified.

The United Kingdom reported that the Government's FRANK drugs information website (talktofrank.com), noted that 4-methylamphetamine has also been sold using the names 'ket phet' or 'phet ket'. However, an online search of these terms yielded no drugs specific information.

Perceived availability at consumer level and price

As noted, in many cases 4-methylamphetamine is being sold as amphetamine. Most consumers are unaware that they are consuming the substance.

⁽³¹⁾ Online sales of new psychoactive substances/'legal highs': summary of results from the 2011 multilingual snapshots. EMCDDA, 2011.

⁽³²⁾ On 18 July 2012, the sites were searched using a range of terms, including '4-methylamphetamine', '4-ma', 'p-tap', 'pal-313', 'buy 4-methylamphetamine', 'buy 4-ma', 'buy p-tap', 'buy pal-313'.

⁽³³⁾ For example: <http://www.trc-canada.com>

⁽³⁴⁾ On the 5 and 21 June 2012 the search engines www.google.sk and www.zoznam.sk were searched using the strings (in Slovak language): kupit '4-methylamphetamine' OR predat '4-methylamphetamine' OR obchod s '4-methylamphetamine' (in English: buy of '4-methylamphetamine' OR sale of '4-methylamphetamine' OR trafficking with '4-methylamphetamine'... 4-MA or p-MA.

An online survey by DAATH (the online forum of the Hungarian Psychedelic Community) and the Hungarian NFP conducted on the forum (daath.hu) between the 15 and 25 June 2012 had 194 persons complete the survey. Only four persons thought that they had ever consumed 4-methylamphetamine. However, in two cases it can be assumed that they consumed a different substance based on the street names they provided for 4-methylamphetamine: 1) 'formek', that is associated with 4-methylethcathinone (4-MEC), and, 2) 'piko' that is associated with methamphetamine. Forum posts on new substances appear quite early on the forum if they are available and consumed in the country. So far no mention of '4-MA' or '4-methylamphetamine' has been found which suggests that the consumption of the 4-methylamphetamine in its own right is not considerable in Hungary.

Information on price was available from Austria, Belgium and the Netherlands. In each case they reported that 4-methylamphetamine was being sold as 'speed'. In Austria four collected samples that contained 4-methylamphetamine (amphetamine was the main active substance present) cost between 15 and 30 €/g. Belgium and the Netherlands reported that the price of 4-methylamphetamine was the same as 'speed' (approximately 10 €/g in Belgium). In other countries where 4-methylamphetamine is sold as amphetamine the price is presumably the same as amphetamine.

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

Racemic 4-methylamphetamine underwent human clinical trials as an anorectic agent ('Aptrol') in the 1950s (see section 3.1 and *Information on toxicity, tolerance and dependence* in section 3.4.1). The proposed daily dosage for Aptrol was 25 or 50 mg three times a day. However, its development and marketing was abandoned for unknown reasons and it was never made commercially available.

Since then, claims have been made in the scientific and patent literature on the use of 4-methylamphetamine as a potential medicine, for example, for the treatment of psychostimulant addiction, an analgesic, and an anti-Parkinson agent. Furthermore, claims have also been made for its use as an intermediate in the synthesis of potential medicines. It should be noted, however, that patents may contain broad claims (for example, the use of 'Markush structures'), and the inclusion of a chemical structure in a patent does not imply that the substance will be developed and/or commercialised as a medicinal product.

There is no information that 4-methylamphetamine is used in the manufacture of a medicinal product in the European Union. However, the collection of information cannot be considered exhaustive in the absence of an EU database on the synthetic routes of all medicinal products ⁽³⁵⁾.

⁽³⁵⁾ I.e. products that have been granted a marketing authorisation, or where an application for a marketing authorisation has been made, or where the marketing authorisation has been suspended.

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

4.1 Marketing authorisation

The 20 Member States, Iceland and Norway which responded to the EMA's information request (see section 2) reported that the new psychoactive substance 4-methylamphetamine has not obtained a marketing authorisation.

4.2 Application for a marketing authorisation

The 20 Member States, Iceland and Norway which responded to the EMA's information request (see section 2) reported that the new psychoactive substance 4-methylamphetamine is not the subject of an application for a marketing authorisation.

4.3 Suspended marketing authorisation

The 20 Member States, Iceland and Norway which responded to the EMA's information request (see section 2) reported that there had been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance 4-methylamphetamine.

5. Summary of findings

- 5.1. 4-Methylamphetamine is a ring-methylated derivative of amphetamine and belongs to the group of synthetic phenethylamines. It was first detected in Belgium in October 2009 and notified to the EMCDDA via the early warning system on 14 December 2009.
- 5.2. Twelve Member States as well as Croatia and Norway reported to Europol and the EMCDDA seizures of 4-methylamphetamine mostly in powder or paste form, ranging from 0.02 g up to 147 kg. A few seizures were in tablet or liquid form.
- 5.3. Samples that contained 4-methylamphetamine typically contained amphetamine and caffeine in varying ratios.
- 5.4. According to information provided to Europol, in recent years multiple illicit production sites and/or other indications related to the production of 4-methylamphetamine have been discovered in the Netherlands.
- 5.5. Seizures related to international trafficking of 4-methylamphetamine have been reported by two Member States with indications of trafficking from a third Member State.
- 5.6. According to information provided to Europol no distinct difference can be made between 4-methylamphetamine and amphetamine in terms of the involvement of organised crime groups, production, trade, and/or users. No specific information was reported on money laundering related to the production and/or trafficking of 4-methylamphetamine. No specific information was received on incidents of violence in connection with the production, wholesale and/or trafficking of 4-methylamphetamine.
- 5.7. Six Member States as well as Croatia control 4-methylamphetamine under drug control or equivalent legislation and two Member States have legislation limiting unauthorised supply of defined or qualifying psychoactive substances. Two Member States control 4-methylamphetamine under medicines legislation.
- 5.8. 4-methylamphetamine is currently not under assessment and has not been under assessment by the UN system.
- 5.9. The precursor known to be used for the manufacture of 4-methylamphetamine, 4-methylbenzyl methyl ketone, is not under international control. It can be potentially used in organic synthesis and appears to be commercially available.
- 5.10. Although some countries noted easy access and availability of 4-methylamphetamine via the Internet, it is unclear to what extent this substance is advertised/sold online.
- 5.11. There is little evidence to suggest a specific demand for 4-methylamphetamine. However, the substance is sold as amphetamine (e.g. as 'speed'). Drug prevalence estimates suggest that about 12.5 million Europeans have tried amphetamines, and about 2 million have used the

drug during the last year. Consequently, this population may be at risk of exposure to 4-methylamphetamine if this substance becomes more widely available.

- 5.12. There have been sixteen deaths and nine non-fatal intoxications related to 4-methylamphetamine, reported in six Member States in a short period of time (reported from October 2011 to the time of writing the report).
- 5.13. There are few published studies on the pharmacology and toxicity of 4-methylamphetamine in animals or human volunteers. It has been speculated that the more pronounced serotonergic action of 4-methylamphetamine compared to amphetamine may diminish the psychoactive effects of the drug leading to repeated dosing.
- 5.14. Racemic 4-methylamphetamine underwent human clinical trials as an anorectic agent ('Aptrol') in the 1950s. However, its development and marketing was abandoned for unknown reasons and it was never made commercially available.
- 5.15. 4-methylamphetamine has no known medical use (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for 4-methylamphetamine in the EU or in the Member States which responded to the EMA.
- 5.16. There are no indications that 4-methylamphetamine is used for other purposes other than in scientific research. At the time of writing the Joint Report, there is no information that 4-methylamphetamine is used in the manufacture of a medicinal product in the European Union. However, the collection of information cannot be considered exhaustive in the absence of an EU database on the synthetic routes of all medicinal products.

6. Conclusions

The health and social risks caused by the manufacture, trafficking and use of 4-methylamphetamine, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA

Annexes

Annex 1 — Main information sources

General

1. EMCDDA and its network of Reitox National Focal Points (NFPs) — standard reporting and replies to Joint Report questionnaire.
2. Europol and its network of Europol National Units (ENUs) — standard reporting and replies to Joint Report questionnaire.
3. EMA and its network of Member States' National competent authorities (NCAs) responsible for human and veterinary medicinal products — replies to Joint Report questionnaire.
4. Scientific articles published in peer reviewed journals.
5. Publications of expert and official bodies.
6. Grey literature.
7. Newspaper and magazine media articles.
8. Internet websites and discussion groups.
9. Personal communication with key informants.

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Annex 2 — Images of 4-methylamphetamine from seizures and collected samples

Country	Image	Description
Austria		Collected sample, analysed in April 2012 0.060 g of a white, paste-like powder, sold as 'speed' (15 €/g). Contents: amphetamine (95 mg/g), caffeine (65 mg/g), 4-methylamphetamine (24 mg/g), ephedrine (16 mg/g). Collecting authority: ChEckiT!
Austria		Collected sample, analysed in April 2012 1.126 g of a white powder, sold as 'speed' (self made). Contents: amphetamine (208 mg/g), caffeine (542 mg/g), 4-methylamphetamine (16 mg/g). Collecting authority: ChEckiT!
Austria		Collected sample, analysed in April 2012 0.03 g of a crumbly white powder, sold as 'speed'. Contents: caffeine (145 mg/g), amphetamine (73 mg/g), 4-methylamphetamine (4 mg/g). Collecting authority: ChEckiT!
Austria		Collected sample, analysed in April 2012 0.103 g of a white paste-like powder, sold as 'speed' (20 €/g). Contents: amphetamine (69 mg/g), caffeine (66 mg/g), ephedrine (27 mg/g), 4-methylamphetamine (19 mg/g). Collecting authority: ChEckiT!
Austria		Collected sample, analysed in May 2012 0.19 g of a white powder, sold as 'speed' (15 €/g). Contents: caffeine (384 mg/g), paracetamol (59 mg/g), 4-methylcathinone (40 mg/g), amphetamine (34 mg/g), 4-methylamphetamine (8 mg/g), unknown substance. Collecting authority: ChEckiT!
Belgium		Seizure, May 2012 82 g of yellow paste, seized in Geraardsbergen. Contents: 4-methylamphetamine (21%), amphetamine (13%) and caffeine (16%). Seizing authority: Belgian Federal Police.
Norway		Seizure, December 2009 120 tablets found in a product labelled 'Green Stinger' which is marketed in the United States as a weight loss supplement. According to the product label it contained 'Ephedra extract' among other ingredients. Contents: analysis revealed that no ephedrine was present. However the analytical data indicated a mix of several compounds: 1-phenylethylamine, 2-phenylethylamine, β-methyl-phenethylamine, N,N-dimethyl-phenethylamine, 4-methylamphetamine, N-benzyl-1-phenylethylamine, yohimbine and caffeine. Seizing authority: Norwegian customs.

Annex 3 — Data of 4-methylamphetamine related fatalities

Country	Date of death	4-Methylamphetamine (mg/L) in blood (1)	Amphetamine (mg/L) in blood (1)	Notes
Belgium	August 2011	1.98 mg/L	1.70 mg/L	THC (0.0024 mg/L) and MDMA (0.23 mg/L) were also detected post-mortem. Analysis of a powder recovered as part of the investigation detected amphetamine sulphate (14%), 4-methylamphetamine (56%), and caffeine (13%).
Belgium	August 2011	1.2 mg/L	0.715 mg/L	Deceased had consumed a powder sold as 'speed'. This case also involved a non-fatal intoxication of another person suspected to have consumed the same powder. Blood concentration of 4-methylamphetamine (0.12 mg/L), no amphetamine detected, sildenafil.
Belgium	September 2011	1.45 mg/L	0.75 mg/L	Olanzapine was also detected post mortem. Analysis of a powder recovered as part of the investigation detected amphetamine, 4-methylamphetamine, and caffeine.
Belgium	February 2012	Detected in post-mortem tissue, concentration not available	Detected in post-mortem tissue, concentration not available	The patient died after cardiorespiratory arrest. Analysis of a powder recovered as part of the investigation detected amphetamine, 4-methylamphetamine and caffeine
Belgium	March 2012	Detected in post-mortem tissue, concentration not available Concentration in ante-mortem femoral blood: 0.62 mg/L	Detected in post-mortem tissue, concentration not available Concentration in ante-mortem femoral blood: 0.480 mg/L	Over the 24 hours prior to death, patient had consumed ketamine, cocaine and amphetamines. Patient developed extreme hyperthermia and died after cardiac arrest. Analysis of a white/yellow powder (< 1 g) recovered as part of the investigation detected amphetamine (11%) and 4-methylamphetamine (25%). Cocaine, benzoylecgonine, and levamisole were also detected in post-mortem tissue (not quantified).
Belgium	July 2012 (2)	Not detected in blood. 4-Methylamphetamine and amphetamine detected in urine (confirmed by GC/NPD)	High concentrations detected in blood	32 year old male

Country	Date of death	4-Methylamphetamine (mg/L) in blood ⁽¹⁾	Amphetamine (mg/L) in blood ⁽¹⁾	Notes
Denmark	December 2010	Detected, concentration not available	Detected, concentration not available	27 year old male. Autopsy/ forensic chemistry suggests that methylamphetamine ⁽²⁾ was cause of death. Amphetamine, ephedrine, methadone, morphine, mCPP and tetrahydrocannabinol were also detected.
Netherlands	2011	1.4 mg/L	0.3 mg/L	
Netherlands	2011	0.98 mg/L	1.7 mg/L	
Netherlands	2011	2.3 mg/L	0.35 mg/L	
Netherlands	2011	2.2 mg/L	0.04 mg/L	MDMA (< 0.01 mg/L) also detected.
Netherlands	2012	0.5 mg/L	0.6 mg/L	
Netherlands	2012	Detected	Detected	While both 4-methylamphetamine and amphetamine were detected further details on this fatality are currently not available.
United Kingdom	October 2010	3.49 mg/L	16.5 mg/L	33 year old male. Sent home from work with flu-like symptoms. Cannabis also detected. No other drugs or alcohol detected.
United Kingdom	May 2011	3.77 mg/L	Not detected	22 year old male. Had taken 'Ecstasy' the night before, insufflated cocaine/'MCat'. Agitated, hot, shaking. Unidentified cathinones and ethanol (270 mg/L) detected. No other drugs detected.
United Kingdom	January 2012	5.8 mg/L	Not detected	Young female found dead. Indications that she had used ketamine and amphetamine. However, neither were detected at post-mortem. Small amount of ethanol (190 mg/L) detected.
United Kingdom	April 2012	Toxicology results not currently available	Toxicology results not currently available	16 year old female. Suspected to have consumed 4-methylamphetamine. Analysis of an off-white damp substance (72 g) seized as part of the investigation detected 4-methylamphetamine and amphetamine (< 1 %). This case also involved a non-fatal intoxication of a 20 year old male (present with the female) who was suspected to have consumed 4-methylamphetamine. However, toxicology results are not currently available.

⁽¹⁾ Most biological samples were blood. However a small number were reported as from urine or tissue samples. This is stated in the table where applicable.

⁽²⁾ Date of analysis of biological sample. Date of death not reported.

⁽³⁾ 2- or 4-Methylamphetamine.

Cataloguing data

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In the European Union, Council Decision 2005/387/JHA provides a legal mechanism for the information exchange (the early warning system), risk assessment and control of new psychoactive substances. When a new substance is detected in a Member State, information on its manufacture, traffic and use is transmitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the European Police Office (Europol) via the Reitox national focal points and Europol national units. The data are also submitted for information to the European Commission and the European Medicines Agency. Under Article 5.1 of the Council Decision where the EMCDDA and Europol, or the Council of the European Union, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information is collated and presented by Europol and the EMCDDA in the form of a Joint Report. This EMCDDA-Europol Joint Report forms the basis on which a decision may be taken by the Council of the European Union on whether or not to launch a risk assessment of the substance.

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The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the hub of drug-related information in Europe. Its mission is to provide the EU and its Member States with 'factual, objective, reliable and comparable information' on drugs, drug addiction and their consequences. Established in 1993, it opened its doors in Lisbon in 1995 and is one of the EU's decentralised agencies. With a 100-strong multidisciplinary team, the agency offers policymakers the evidence base they need for drawing up drug laws and strategies. It also helps professionals and researchers pinpoint best practice and new areas for analysis. As well as gathering information on the demand and reduction of the demand for drugs, the agency in recent years has extended its monitoring and reporting on drug supply, supply reduction and illicit drug markets.

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