European Monitoring Centre
for Drugs and Drug Addiction

RISK ASSESSMENTS 10

ISSN 1725-4493

4-Methylamphetamine (4-MA)

Report on the risk assessment of 4-methylamphetamine in the framework of the Council Decision on new psychoactive substances

About this series

EMCDDA Risk Assessments are publications examining the health and social risks of individual new psychoactive substances.

The Risk Assessment Report consists of an analysis of the scientific and law enforcement information available on the new psychoactive substance under scrutiny and the implications of placing it under control. It is the outcome of a meeting convened under the auspices of the EMCDDA Scientific Committee.

This process is part of a three-step procedure involving information exchange/early warning, risk assessment and decision-making in the framework of the Council Decision 2005/387/JHA.

Contents

Acknowledgements

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

- the members of the extended Scientific Committee of the EMCDDA; the advisers to the Scientific Committee and the invited external experts who took part in the risk assessment meeting;
- the Early-warning system correspondents of the Reitox national focal points (NFPs);
- the services within each Member State that collected the raw data for the risk assessment;
- Europol, the European Medicines Agency (EMA) and the European Commission;
- Dr Paul Dargan, Dr David Wood and Dr István Ujváry for preparing the technical review on the pharmacotoxicological, sociological and criminological evidence and public health risks of 4-methylamphetamine;
- Fazlin Mohd Fauzi and Dr Andreas Bender for conducting the computational analysis to assess the pharmacology of 4-methylamphetamine;
- EMCDDA colleagues: Paul Griffiths, Anabela Almeida and Katarzyna Natoniewska, who edited and managed the production of the publication.

EMCDDA project leaders: Roumen Sedefov, Michael Evans-Brown, Andrew Cunningham, Ana Gallegos

Foreword

It is with great pleasure that I present this comprehensive publication, which contains the data and findings of the risk assessment on the new psychoactive substance, 4-methylamphetamine, that was conducted by the Scientific Committee of the EMCDDA.

Concerns over the availability and use of this stimulant drug in the European Union led to an assessment of the health and social risks posed by the substance, and, consequently, its control across the EU Member States. The decision of the Council of the European Union to control 4-methylamphetamine, on the initiative of the European Commission, marks the final stage in the three-step process set up by Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances that allows the European Union to respond to potentially threatening new psychoactive substances.

Over the past few years much focus, rightly, has been given to the 'legal highs' phenomenon. Here, new psychoactive substances that mimic the effects of controlled drugs have been sold, often in attractive packaging, through head shops and the internet. The continued growth of this market has seen the issue of new psychoactive substances develop into an increasingly complex policy challenge that is now of major international concern. The chemical industries in China and India have been the focus of much discussion over the source of the bulk chemicals used in these products. Yet, the case of 4-methylamphetamine serves as a stark reminder to us that new drugs continue to be produced in Europe (albeit likely that the precursors are sourced from third countries) and sold directly on the existing illicit drug market, rather than the all too familiar open market for 'legal highs' that is subject to almost daily media reports.

Crucial to understanding the reasons for taking action on 4-methylamphetamine are, first and foremost, the reports of acute toxicity that included 21 associated deaths, but also the large-scale production and trafficking of the drug in Europe. In this respect 4-methyl-amphetamine also serves as a reminder of why a multi-disciplinary approach to the new drug phenomenon is essential, in this case with both law enforcement and health agencies playing a central role in helping to solve the riddle of where this drug came from, who was making it, who was distributing it, and the harms it posed to users. As it turned out, it was the same organised crime groups involved in the production of amphetamine that were responsible for the emergence of 4-methylamphetamine and its subsequent sale as amphetamine, ultimately placing at risk the amphetamine using population.

I would like to acknowledge the contribution and thank the members of the extended Scientific Committee of the EMCDDA, the EU Member States experts, the European Commission, Europol, the European Medicines Agency and the EMCDDA staff who participated in the risk assessment meeting, which took place on 16 November 2012 at the EMCDDA in Lisbon. The resulting report is a valuable contribution at European level, which gives clear support to political decision-making. Of course none of this would have been possible without the excellent work undertaken by the networks of the EMCDDA, Europol and the European Medicines Agency — the Reitox national focal points, Europol National Units, and the national competent authorities responsible for medicinal products — who, as ever, played an essential role in collecting and providing national data, thus ensuring a truly multidisciplinary effort.

Wolfgang Götz
Director, EMCDDA

Introduction

The appearance of 4-methylamphetamine on the amphetamine market in 2009 was something of a mystery. One inevitable question posed by those working in the new drugs field was whether, like many of the designer drugs that had appeared on the European market over the past two decades, 4-methylamphetamine was produced by accident or design. Was it deliberately manufactured because it was not covered by national or international law, or was it an attempt to circumvent legislation on precursor control?

The reason why 4-methylamphetamine emerged is still unclear, although tellingly, unlike the precursor used to manufacture amphetamine, the precursor for 4-methyl-amphetamine, 4-methyl-BMK, is not under international control and appears to be commercially available. This did not change the fact that a new drug had emerged onto the European market for which there was limited information on its effects, including potential for harm. Compounding this was the fact that 4-methylamphetamine did not have to catch on first with users: its diffusion was assured as, unknown to both dealers and users, it was being sold as amphetamine on one of the largest established stimulant drug markets in Europe. This was a concern, given the fact that 21 deaths were associated with the substance at the time the risk assessment meeting was conducted.

To add to these concerns, it was soon found that the same organised crime groups that were involved in amphetamine were also responsible for the production, trafficking and distribution of the 4-methylamphetamine. By November 2012 the drug had been detected in 15 Member States, with production reported in one Member State.

4-Methylamphetamine belongs to the phenethylamine family and is chemically very close to amphetamine. Nonetheless, the literature review highlighted key differences in the pharmacology of the two substances. This included different effects on the monoaminergic system particularly in respect to 4-methylamphetamine's actions on serotonin. In addition, concerns were raised over the possibility of caffeine to potentiate the toxicity of 4-methylamphetamine, which, given that the two substances were generally found in combination—and often together with amphetamine—requires further examination.

The absence of information and research findings has been a challenge for all risk assessments conducted by the Scientific Committee. Therefore, the risk assessment conclusions are inevitably based on partial knowledge and, consequently, are tentative. Many of the questions posed by the lack of evidence on the health and social effect of 4-methylamphetamine could be answered by further research. Areas where additional information would be useful include studies on: metabolic pathways; clinical patterns of acute and chronic toxicity in humans; potential interactions with other substances (in particular caffeine and amphetamine); the dependence and abuse potential; and the social risks associated with its use. Both intended and unintended consequences of a decision to control 4-methylamphetamine should also be considered, as outlined in the present report.

Despite the challenges, the risk assessment exercise under Council Decision 2005/387/JHA remains a unique element of the European action on new drugs and constitutes an important instrument to support decision-making at the level of the European Union. It can also be viewed as a useful mechanism to provide added value and support to national efforts in this area, and may serve as a good example of an evidence-based approach to sensitive policy issues.

Finally, I would like to thank all our colleagues from the extended Scientific Committee for sharing their knowledge and insights, which contributed to a stimulating and productive discussion. Also, I would like to express my appreciation to the external experts and to the EMCDDA staff who worked hard before, during and after the meeting to prepare and finalise the reports. I hope that these combined efforts will be appreciated by those to whom this report is addressed.

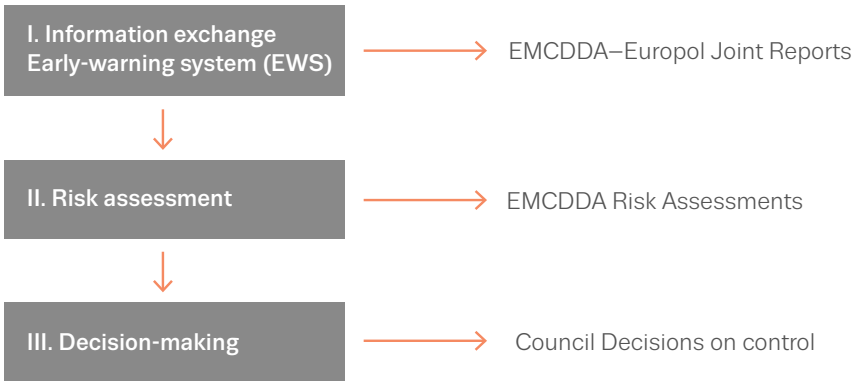
Professor Dr Gerhard Bühringer
Vice-Chair of the Scientific Committee of the EMCDDA

EMCDDA actions on monitoring and responding to new drugs

The EMCDDA has been assigned a key role in the detection and assessment of new drugs in the European Union under the terms of a Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances. It establishes a mechanism for the rapid exchange of information on new psychoactive substances and provides for an assessment of the risks associated with them in order to permit the measures applicable in the Member States for the control of narcotic and psychotropic substances to be applied also to new psychoactive substances.

The three-step process involves information exchange/early warning, risk assessment and decision-making (see below). More detailed information can be found in the section 'Action on new drugs' of the EMCDDA's website: www.emcdda.europa.eu/activities/action-on-new-drugs

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances



EMCDDA–Europol Joint Report on 4-methylamphetamine: a summary

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

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 available on 4-methylamphetamine satisfies the above criteria. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report on 4-methylamphetamine as stipulated by Article 5.1 of the Decision. Accordingly, the Reitox NFPs, the European National Units (ENUs), the EMA and WHO were formally asked to provide the relevant information within six weeks from the date of the request, i.e. by 2 July 2012.

The resulting Joint Report on 4-methylamphetamine was submitted to the Council, the Commission and the European Medicines Agency (EMA) on 30 July 2012. The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in 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.

The full text of the Joint Report can be found at:

www.emcdda.europa.eu/publications/joint-reports/4-methylamphetamine

Risk Assessment Report of a new psychoactive substance: 4-methylamphetamine

Introduction

This Risk Assessment Report presents the summary findings and the conclusions of the risk assessment carried out by the EMCDDA's extended Scientific Committee of the new psychoactive substance 4-methylamphetamine. The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the *Operating guidelines for risk assessment of new psychoactive substances* (EMCDDA, 2010) ([1]). It is written as a stand-alone document that presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion of the report summarises the main issues addressed and reflects the opinions held by the members of the Committee. A more detailed 'Technical report on 4-methylamphetamine' is annexed to this report (Annex 1).

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

There is emerging evidence that the new psychoactive substance 4-methylamphetamine has appeared on the drug market in Europe. In response to this, in compliance with the provisions of Article 5 of the Decision, on 31 July 2012, the EMCDDA and Europol submitted to the Council, the Commission and the European Medicines Agency (EMA) a Joint Report on the new psychoactive substance 4-methylamphetamine ([5]). Taking into account the conclusion of the Joint Report and in accordance with Article 6 of the Decision, on 24 September 2012 the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of 4-methylamphetamine was convened under the auspices of the EMCDDA's Scientific Committee with the participation of three additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts are from scientific fields that are either not represented, or not sufficiently represented, on the Scientific Committee, and whose contribution is necessary for a balanced and adequate assessment of the possible risks of 4-methylamphetamine, including health and social risks. Furthermore, two experts from the Commission, one expert from Europol and one expert from the EMA participated in the risk assessment. The meeting took place on 16 November 2012 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMA. A full list of the extended Scientific Committee and the list of participants attending the risk assessment meeting are included at the end of this publication.

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

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

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

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

([5]) www.emcdda.europa.eu/publications/joint-reports/4-methylamphetamine

For the risk assessment, the Scientific Committee considered the following:

(i) Technical report on 4-methylamphetamine (November 2012);
(ii) Computational analysis on the pharmacology of 4-methylamphetamine (September 2012) — EMCDDA-commissioned study by Cambridge University;
(iii) EMCDDA–Europol Joint Report on a new psychoactive substance 4-methylamphetamine ([6]);
(iv) Scientific articles, official reports, grey literature and Internet drug user discussion forums;
(v) *Operating guidelines for risk assessment of new psychoactive substances* (EMCDDA, 2010) ([7]);
(vi) Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances.

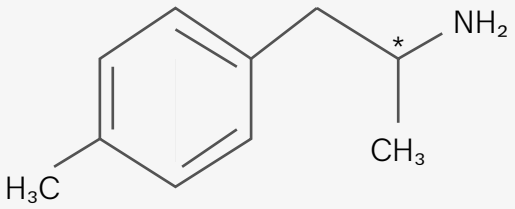
Physical and chemical description of 4-methylamphetamine and its mechanisms of action, including its medical value

4-Methylamphetamine is a synthetic phenethylamine stimulant. It is a ring-methylated derivative of amphetamine. It has many synonyms (listed in Annex 1) but the systematic (International Union of Pure and Applied Chemistry, IUPAC) name of 4-methylamphetamine is 1-(4-methylphenyl)propan-2-amine. It is also important to distinguish 4-methyl-amphetamine from the substance commonly known as methamphetamine ('meth') that is correctly called *N*-methylamphetamine.

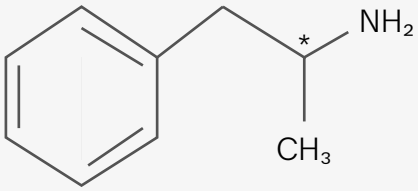
The molecular structure, empirical formula, and molecular weight of 4-methylamphetamine are shown below (asterisk indicates chiral centre). The structure of amphetamine is also shown for reference.

The free base of 4-methylamphetamine is a nearly colourless liquid with an amine-like odour. The hydrochloride and sulfate salts are white or lightly coloured crystals. It is the salt form that is predominantly detected in seizures and collected samples ([8, 9]).

4-Methylamphetamine has predominately been seized in powder and paste form, but liquids containing the substance have occasionally been encountered. A large proportion of the seized powders and pastes also typically contain amphetamine and caffeine in widely varying ratios. Solutions of the drug have also been seized, some of which contained amphetamine and/or caffeine ([10]). Tablets have been encountered infrequently. Additionally, other active substances including 4-methylethcathinone (4-MEC), methylenedioxymethylamphetamine (MDMA) and ketamine have been found in a small number of seizures and collected samples. There has been one report of 4-methylamphetamine detected in a commercial product called 'Green Stinger'. A product bearing this name is sold on the internet as an 'ephedrine weight-loss product' (4-methylamphetamine was not listed as an ingredient on this product).



4-Methylamphetamine



Amphetamine

Empirical formula: $C_{10}H_{15}N$

Molecular weights: 149.23 (base); 185.69 (HCl salt); 396.54 ($(C_{10}H_{15}N)_2 \cdot H_2SO_4$ salt, i.e. Aptrol, see below).

([6]) http://www.emcdda.europa.eu/publications/joint-reports/4-methylamphetamine
([7]) http://www.emcdda.europa.eu/html.cfm/index100978EN.html

([8]) '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.).
([9]) For the sake of brevity, the term '4-methylamphetamine' is used throughout the text although it is the hydrochoride or sulfate salt that is seen in seizures and collected samples. For methodological reasons, and because 4-methyl-amphetamine is frequently mixed with other salt-forming stimulants, the inorganic acid is usually not specified by forensic laboratories that analyse samples.
([10]) Germany reported a seizure of a nasal spray that contained a colourless, clear liquid containing amphetamine, 4-methylamphetamine and caffeine. As hydrochlorides, the amphetamines are readily water-soluble and it is possible that the spray was home-made from a powder or paste.

Analysis using gas chromatography (GC) and liquid chromatography (LC) coupled with mass spectrometry (MS) is straightforward. Though the 2-, 3- and 4- positional isomers have virtually identical mass spectra, they can be distinguished based on their retention time. It should be noted that 4-methylamphetamine (and its positional isomers) have the same empirical formula as *N*-methylamphetamine. This may present an analytical issue if using accurate mass spectrometry without subsequent fragmentation. The infrared and nuclear magnetic resonance spectra of the positional isomers are different. Analytical reports of 4-methylamphetamine of seized, collected and biological samples have not indicated the presence of the 2- or 3- positional isomers nor are data available on the enantiomeric composition of 4-methylamphetamine found in these samples ([11]).

In the 1950s, 4-methylamphetamine was studied by Smith, Kline & French Laboratories as a potential anorectic medicine under the trade name Aptrol ([12]). However, its development and marketing was abandoned for unknown reasons and it was never made commercially available. Claims have been made in the scientific and patent literature on the use of 4-methylamphetamine as a potential medicine and as an intermediate in the synthesis of potential medicines. It should be noted, however, that patents may contain broad claims and the inclusion of a chemical structure in a patent does not mean that the substance will be developed and/or commercialised as a medicinal product.

4-Methylamphetamine has no established or acknowledged medical value or use (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for 4-methylamphetamine in the European Union or in the Member States that responded to the EMA's information request launched under Article 5 of the Decision. There is no information that 4-methylamphetamine is used for the manufacture of a medicinal product or an active pharmaceutical ingredient (API) of a medicinal product in the European Union. However, it should be noted that there is no European Union database on the synthetic routes of all registered medicinal products. The use of 4-methylamphetamine cannot be ruled out with certainty.

4-Methylamphetamine is used as an analytical reference standard and in scientific research (in the latter case, often in combination with amphetamine and related compounds, some of which are under international control). There are no other indications that 4-methylamphetamine is currently being used for any other legitimate purpose. There are no known uses of 4-methylamphetamine as a component in industrial, cosmetic or agricultural products.

Data on the pharmacokinetics of 4-methylamphetamine are limited to one study reported in 1950 of six volunteers suggesting anorectic effects lasting 6–10 hours and significant hypertension lasting 20–30 minutes, both of which were dose dependent. In addition, one user reported 'psychedelic effects' with a 'plateau at two hours, and baseline at four hours'. There is no published information on the biotransformation (metabolism) of 4-methylamphetamine in animals or humans. It is reasonable to assume, however, that metabolism follows the biochemical pathways established for structurally related substances (such as mephedrone).

There have been a number of studies in animals that have investigated the pharmacodynamics of 4-methylamphetamine. Typically these have compared it to amphetamine and/or other ring-substituted amphetamines. These studies suggest that 4-methylamphetamine has effects on stimulating the release and inhibiting the reuptake of serotonin, dopamine and noradrenaline in the brain. Overall, in comparison to amphetamine, it appears to have greater effects on serotonin reuptake than dopamine or noradrenaline. Furthermore, 4-methylamphetamine has been found to be more potent than amphetamine in inhibiting animal brain monoamine oxidase (MAO) leading to elevated dopamine, and, in particular, serotonin levels both *in vitro* and *in vivo*.

One animal study demonstrated that pre-treatment with caffeine potentiated the anorectic effects of 4-methylamphetamine. This effect was not seen with amphetamine. However, no studies have investigated the co-administration of 4-methylamphetamine with amphetamine and/or caffeine, therefore there are no data on the possible drug interactions. This is important, given the fact that the most prevalent situation observed in the illicit market involves all three substances together.

Animal models suggest that although 4-methylamphetamine has a similar median lethal dose (LD_{50}) to amphetamine, there is variation based on the model used and the route of administration. One study in an animal model also suggests that the pharmacological spectrum of 4-methylamphetamine is more LSD-like than that of amphetamine, though much less active than 2,5-dimethoxy-4-methylamphetamine (DOM).

4-Methylamphetamine was the least likely to cause self-administration in an animal study that compared the self-administration of 4-methylamphetamine with amphetamine, 3-methylamphetamine, 3-fluoroamphetamine and 4-fluoroamphetamine.

([11]) Published biological studies, including toxicological ones, have used the racemic mixture. It is not known whether there are substantial differences between the pharmacology of 4-methylamphetamine enantiomers.

([12]) The trade name Aptrol originally referred to the sulfate salt comprised of two moles of 4-methylamphetamine and one mole of sulfuric acid.

There are no published studies that have formally assessed the psychological and/or behavioural effects of 4-methylamphetamine in humans.

A human volunteer study and a clinical trial conducted in the 1950s have shown that 4-methylamphetamine is associated with hypertension, anorexia, nausea, perspiration, gastric distress, coughing, vomiting, headache, pruritis and palpitations. Additionally, unconfirmed user reports, some of which involved multiple co-used substances, suggest similar adverse effects as well as insomnia, paranoia, anxiety, depression and 'nervousness and stimulation resembling ephedra'.

Chemical precursors that are used for the manufacture of 4-methylamphetamine

The synthesis of 4-methylamphetamine requires similar equipment and chemical expertise to those needed for the manufacture of other amphetamines. Most of the published methods for the synthesis of 4-methylamphetamine rely on the reductive amination of the precursor 4-methylbenzyl methyl ketone (4-methyl-BMK) ([13]) and, in particular, use the Leuckart reaction. These reactions are feasible in an amateur laboratory setting and do not require sophisticated equipment. Although the methods used to produce 4-methyl-amphetamine currently on the illicit drug market are not specifically known, the presence of detectable levels of 4-methyl-BMK in some samples indicates this is one of the precursors used. Studies conducted on seized samples and investigations at illicit manufacturing sites suggest that the methods of synthesis noted above have been used.

The relevant precursor 4-methyl-BMK can be potentially used in general organic synthesis. It appears to be commercially available and is not under international control.

It has been hypothesised that the presence of 4-methylamphetamine in amphetamine samples may be due to changes in the availability of precursors used for the illicit synthesis of amphetamine.

([13]) Other chemical names are 4-methylphenylacetone and 1-(4-methylphenyl) propan-2-one. The CAS Registry Number for this ketone is 2096-86-8.

Health risks associated with 4-methylamphetamine

Individual health risks

The assessment of individual health risks includes a consideration of the acute and chronic toxicity of 4-methyl-amphetamine, as well as its dependence potential, and its similarities to and differences from other chemically related stimulants.

There are limited data available on the main routes of administration for 4-methylamphetamine. However, a small number of user reports, together with extrapolation from the routes of administration for amphetamine, suggest that these may include oral ingestion (swallowing), nasal insufflation (snorting), intramuscular and intravenous injection, and rectal insertion. It is likely, given that 4-methylamphetamine is sold and used as amphetamine, that the most common routes of use reflect those used for amphetamine.

Systematic data are not routinely collected in Europe on acute toxicity related to 4-methylamphetamine. There are no recent studies. There has only been one case study published on an individual using 4-methylamphetamine, 4-methylmeth-amphetamine and alcohol. There are also limited data from a volunteer study and a clinical trial investigating 4-methylamphetamine. The effects described are similar to those seen with other stimulant drugs such as amphetamine.

Adverse effects reported by users include headache, heavy sweating, nausea, abdominal pains, high blood pressure, flutter, headache, paranoia, hallucinations, anxiety and depression, empathy and euphoria, with post-use effects such as insomnia, 'cognitive disorder' and 'mood disorder'. These are based on self-reports, and a limitation is that users may not have used 4-methylamphetamine. In addition, they may have used other substances which may account for some or all the described effects.

The adverse effects reported in the volunteer study of 4-methylamphetamine administration were dose-related hypertension and anorectic effects, nausea, sweating, gastric distress, hypersalivation, expectoration and coughing. The adverse effects reported in the clinical trial of 4-methyl-amphetamine as an anorectic agent were headache, pruritis and palpitations. There was no significant difference between 4-methylamphetamine and placebo in terms of effects on blood pressure and heart rate. However, the limitations in the design of these studies restrict the interpretation of these adverse effects.

Although there have been reports of detection of 4-methylamphetamine in non-fatal intoxications, there are insufficient clinical details in these reports to be able to determine the clinical pattern of acute toxicity seen. Most exposures to 4-methylamphetamine appear to occur where individuals have used 'speed' (amphetamine), i.e. users are unaware that they have taken 4-methylamphetamine. Therefore, it may be the case that the acute toxicity related to the use of 4-methylamphetamine is underreported.

To date, there have been a total of 21 fatalities from four Member States (Belgium, Denmark, the Netherlands and the United Kingdom) where 4-methylamphetamine alone or in combination with one or more other substance has been detected in post-mortem samples, especially amphetamine. It is not possible to determine with certainty the role of 4-methylamphetamine in these fatalities from the available information. However, in some cases 4-methylamphetamine was the predominant drug detected, with levels comparable to those found in some amphetamine deaths.

While there are insufficient clinical details in the non-fatal and fatal intoxications to be able to determine the clinical pattern of acute toxicity, evidence of hyperthermia has been reported.

No studies have been published investigating the potential for chronic 4-methylamphetamine toxicity in humans, including reproductive toxicity, genotoxicity and carcinogenic potential. However, there has been one limited animal study investigating the sub-acute and chronic toxicity suggesting that 4-methylamphetamine was not associated with histological changes in a number of organs.

In summary, from the limited data sources available, it appears that the acute toxicity of 4-methylamphetamine is similar to other stimulants. However, there is some evidence that in combination with other substances including amphetamine and caffeine, there may be a higher risk of overall enhanced toxicity. While there have been reports of fatalities where 4-methylamphetamine was detected, it is difficult to determine the role of the drug in these fatalities from the available information. However, 4-methyl-amphetamine was recorded as the cause of death in certain cases.

Public health risks

The public health risks associated with 4-methylamphetamine may be categorised in terms of the extent, frequency and patterns of use; availability and quality of the drug; information availability and levels of knowledge amongst users; and negative health consequences.

As noted, in almost all cases 4-methylamphetamine is being sold as amphetamine and most users will be unaware that they are consuming the substance.

In general, the quality (purity) of 4-methylamphetamine appears to be variable but the situation is made more complex by the presence of amphetamine and/or caffeine in many samples. In many cases, seized samples have not been quantitatively analysed and so the relative proportions of active substances are not known. In cases where the amount of 4-methylamphetamine has been determined, it has varied from trace or low amounts with a small number of reports where 4-methylamphetamine is reported as the main or sole component of the mixture. Data from samples collected from users in the Netherlands from 2010 to mid-2012 found that between 7 and 13 % of 'speed' samples contained both 4-methylamphetamine and amphetamine, with a smaller proportion (less than 2 %) containing 4-methylamphetamine only (the presence of caffeine was not reported). There has also been a small number of samples containing 4-methylamphetamine where active substances other than amphetamine and caffeine have been detected.

There are limited data available on the prevalence of use of 4-methylamphetamine. Non-representative studies of 'psychedelic users' in Hungary and attendees at gay-friendly nightclubs in London, United Kingdom suggest self-reported lifetime use of 4-methylamphetamine of 2.1 and 5.8 % respectively. It is possible that in at least some cases, participants reporting the use of 4-methylamphetamine were actually referring to 'methamphetamine'. Given that most exposures to 4-methylamphetamine occur when users attempt to use amphetamine, it is worth noting that drug prevalence estimates suggest that about 2 million Europeans have used amphetamines during the last year ([14]). Consequently, populations using amphetamines may be at risk of exposure to 4-methylamphetamine if this substance remains on the illicit drug market.

It is likely that 4-methylamphetamine will be used in similar environments as amphetamine. These include nightclubs/discos, bars/pubs, outdoor music festivals and home environments. The route of supply of 4-methylamphetamine is through street-level drug dealers.

Aside from what is known from the limited studies noted above, there is no further information on the nature and extent of health consequences. In particular there are no European data on acute emergency department presentations related to 4-methylamphetamine toxicity. One study has noted the

([14]) Amphetamines is a generic term that includes both amphetamine and methamphetamine — and it is important to note that there have been no indications that 4-methylamphetamine has been sold as 'methamphetamine'.

detection of 4-methylamphetamine in five serum samples of vehicle drivers in Germany. However, additional information is not available to allow further assessment.

4-Methylamphetamine is not commercially marketed through Internet shops aimed at users (i.e. those selling 'legal highs' or 'research chemicals'). One Member State noted that 4-methylamphetamine was being offered for sale in classified adverts on the Internet in October 2011. Some websites/web portals listed chemical suppliers that could purportedly offer 4-methylamphetamine for sale. No countries reported seizures or collected samples linked to sale of the drug on the Internet. Norway reported a single seizure by customs authorities in 2009 where 4-methylamphetamine was detected in a 'weight loss' product and they noted that this product is offered for sale on the Internet. 4-Methyl-amphetamine is, however, available from Internet sites as an analytical reference standard or for scientific research purposes.

Social risks associated with 4-methylamphetamine

There is a lack of data upon which to allow sufficient reasoned discussion on the social risks associated with 4-methyl-amphetamine. However, given that it is sold as amphetamine it is possible to draw inferences from what is known about the amphetamine market.

The European amphetamine market can be characterised by two main patterns of use. The biggest group of users are generally episodic or occasional users of the drug, most of whom are relatively well-integrated socially. Here, patterns of use among this group will vary from occasional experimental use (only once or twice) to regular episodic but intensive periods of use. A second, more chronic, pattern of use can also be found in some countries, notably Norway, Latvia, Sweden and the United Kingdom. This pattern of use is characterised by long-term injection of amphetamine, which is often in high dose. These users tend to be more socially marginalised and suffer from more chronic health problems.

There have been no studies to determine the impact of 4-methylamphetamine use on educational outcomes such as attendance, concentration and exam performance. Similarly, there are no data on the effect of 4-methylamphetamine use on performance/attendance at work, career progression, effects on personal relationships or neglect of family.

Sweden has reported six cases where crimes were associated with 4-methylamphetamine as a factor; however, details of these cases are not available.

It is not possible at this time to estimate whether 4-methylamphetamine is associated with higher healthcare costs than other stimulant drugs given the lack of data.

As noted, 4-methylamphetamine has been identified in the serum of a small number of vehicle drivers. The significance of this finding is unclear.

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

The available information suggests that 4-methylamphetamine is produced and trafficked by the same organised crime groups that are involved with the manufacture and trafficking of amphetamine. There is no specific information that criminal groups are knowingly and systematically involved in the manufacture, trafficking and/or distribution of 4-methylamphetamine.

The only Member State to have reported the detection of illicit manufacture of 4-methylamphetamine is the Netherlands. In 2010, 4-methylamphetamine was detected in four illicit amphetamine laboratories. In August 2011, traces of 4-methylamphetamine were found at an amphetamine crystallisation site. In 2012, small amounts of 4-methyl-amphetamine were detected in two cases related to the illicit production of the amphetamine precursor benzyl methyl ketone (BMK) from the non-controlled pre-precursor alpha-phenylacetoacetonitrile (APAAN). In one of the cases, in which 600 kg of APAAN was seized at a trailer park, the presence of 4-methyl-BMK was also detected (in residues) at the site. Information from Dutch police suggests that some producers believed they were using BMK to produce amphetamine. However, it appears they were actually using 4-methyl-BMK and as a result were inadvertently producing 4-methylamphetamine.

There are a number of reports where 4-methylamphetamine has been trafficked from the Netherlands to Germany, France and the United Kingdom. These seizures amount to more than 240 kg of powder/paste and 9 kg of liquid containing 4-methylamphetamine. The largest of these seizures was 147 kg of paste also containing amphetamine and caffeine. This was intercepted in France en route to the United

Kingdom. Furthermore, French authorities intercepted one seizure en route to Spain.

There is no information to suggest that distribution networks other than those established for amphetamine are being used. It does not appear, based on the information available to the ECMDDA and Europol, that the manufacture, trafficking, and distribution of 4-methylamphetamine impacts on other existing psychoactive substances or new psychoactive substances (apart from amphetamine).

In summary, some organised crime groups involved in the manufacture, trafficking, and distribution of amphetamine (and in some cases its main precursors) are also involved in the manufacture, trafficking and distribution of 4-methylamphetamine.

Information on any assessment of 4-methylamphetamine in the United Nations system

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 UN Single Convention on Narcotic Drugs and the 1971 UN Convention on Psychotropic Substances. 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.

Description of the control measures that are applicable to 4-methylamphetamine in the Member States

4-Methylamphetamine is not listed for control in the 1961 UN Single Convention on Narcotic Drugs and the 1971 UN Convention on Psychotropic Substances (together 'UN drug conventions').

Nineteen Member States do not control 4-methylamphetamine under legislation derived from their obligations under the UN drug conventions. The remaining eight Member States (Cyprus, Denmark, France, Germany, Ireland, Lithuania, the Netherlands and the United Kingdom) and Croatia control 4-methylamphetamine under legislation derived from the obligations under the UN drug conventions. In Cyprus, Ireland, Lithuania and the United Kingdom, 4-methylamphetamine is controlled using a generic definition of phenethylamines.

Belgium and Italy have noted that they intend to introduce such controls. 4-Methylamphetamine is not controlled in Norway or Turkey.

In addition, Austria and Hungary have legislation prohibiting the unauthorised supply of defined or qualifying psychoactive substances and control 4-methylamphetamine within a generic definition of phenethylamines.

Finland uses their medicines legislation to control 4-methylamphetamine.

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

Options for control and the possible consequences of the control measures

Under Article 9.1 of the Decision, the option for control that is available at European Union level is for the Member States to submit the new psychoactive substance 4-methyl-amphetamine to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the 1971 UN Convention on Psychotropic Substances. There are no specific European studies on the possible consequences of such control measures. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control could facilitate the detection, seizure and monitoring of 4-methylamphetamine related to its illegal manufacture, trafficking and use. In so doing, it could facilitate international cooperation between the judicial authorities and law enforcement agencies. As 4-methylamphetamine is already present in the illegal market being sold as amphetamine, it is unlikely that control measures would increase the size of the illicit amphetamine market with the increased risk of associated criminal activity, including organised crime.
- A health consequence that may result from control measures is the benefit brought about by the presumed reduction in availability and use.

- Control measures would not necessarily imply additional costs related to law enforcement, criminal justice, forensic analysis, testing, etc., as amphetamine is already controlled in the Member States.
- It is not possible to predict whether there will be health or social consequences from any substance(s) that might be manufactured as a result of this control, such as other non-controlled substituted amphetamines.
- At present, there is no reason to expect that this control would impact on current or future research by the pharmaceutical or chemical industries.

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

Aside from the option for control under those stipulated in Article 9.1 of the Decision, other options for control may be available to Member States. As noted, some Member States have regulated 4-methylamphetamine under medicines legislation and some have imposed restrictions on the importation and supply of the substance.

Although outside the scope of the Decision, it may be important to monitor the availability of the precursors used for the manufacture of 4-methylamphetamine (e.g. 4-methyl-BMK). Reducing the availability of precursors may limit the manufacture and availability of the drug.

Conclusion

4-Methylamphetamine is a stimulant drug. It is a synthetic ring-methylated derivative of amphetamine. It is found mostly as a powder but also as a paste, in liquids and in tablets. It has no established or acknowledged medical use (human or veterinary) in the European Union. There are no indications that it may be used for any other purpose aside from as an analytical reference standard and in scientific research (this is often in combination with amphetamine and related compounds, some of which are under international control).

It has emerged on the illicit amphetamine market where it is sold and used as amphetamine. This appears to be due to changes in the supply of precursor materials used in the manufacture of amphetamines. It is often detected in mixtures along with amphetamine and/or caffeine. The main precursor for its synthesis, 4-methyl-BMK, is commercially available. There has been one report of where 4-methyl-amphetamine was detected in a 'dietary supplement' sold as a 'weight loss' product.

The physical effects of 4-methylamphetamine have rarely been reported by users as they are typically unaware they have taken the substance. However, the few reports that are available suggest stimulant-type effects. There are no published formal studies assessing the psychological and/or behavioural effects of 4-methylamphetamine in humans. In animal studies, 4-methylamphetamine has been shown to affect the monoaminergic systems differently from amphetamine, in particular in respect to its action on serotonin. Limited available data in humans suggest that the adverse effects of 4-methylamphetamine include hyperthermia, hypertension, anorexia, nausea, perspiration, gastric distress, coughing, vomiting, headache, pruritis, palpitations, insomnia, paranoia, anxiety and depression.

4-Methylamphetamine is generally found in combination with amphetamine and/or caffeine. There are no data to be able to determine the clinical significance and risks associated with these combinations. However, there are concerns about the increased risks posed by using this substance in combination with other psychoactive substances, in particular with respect to amphetamine and caffeine.

Prevalence specific to 4-methylamphetamine is difficult to estimate. There is no specific demand for the substance. It is sold as amphetamine, with users unaware they are consuming it. Thus, it can be assumed that the amphetamines-using population — an estimated 2 million Europeans during the last year — may be at risk of exposure to the drug.

The available data from animal studies indicate that the risk of acute toxicity for 4-methylamphetamine when administered on its own is similar to that of amphetamine. 4-Methyl-amphetamine has been detected in 20 non-fatal intoxications or drug-related offences. However, there is insufficient information in these cases to be able to characterise the pattern of toxicity in humans. The chronic health effects, including reproductive toxicity, genotoxicity and carcinogenic potential in humans are unknown.

4-Methylamphetamine has been detected in 21 fatalities in four Member States, either alone or in combination with one or more substances. The results of the statutory investigations (e.g. coroners' findings) into most of the deaths are not available. However, it has been mentioned in the cause of death in some cases.

Current data are not sufficient to determine the relative dependence-producing potential of 4-methylamphetamine.

4-Methylamphetamine has been detected in 15 Member States and two other countries that report to the EMCDDA. It has the potential to diffuse to other countries and this may constitute a health and social threat. Diffusion appears to be a

function of precursor availability rather than demand from users.

The social consequences associated with the use of any drug are likely to be influenced by a number of factors. However, data specific to 4-methylamphetamine are extremely limited, although there appears to be no specific user demand for the drug.

4-Methylamphetamine appears to be sold on the illicit amphetamine market by street-level drug dealers. Organised crime is involved in manufacture, trafficking and supply.

Many of the questions posed by the lack of evidence on the health and social risks of 4-methylamphetamine, as for any new psychoactive substance, could be answered through further research. Areas where additional information would be useful include: metabolic pathways for 4-methylamphetamine; acute and chronic clinical patterns of toxicity in humans; the potential interaction between 4-methylamphetamine and amphetamine and/or caffeine as well as other substances (including medicines that affect the serotonergic system, e.g. selective serotonin reuptake inhibitors); the dependence and abuse potential; and the social risks associated with its use.

The Committee notes that a decision to control this drug has the potential to bring with it both positive and negative consequences. Potential positive consequences include reduced levels of manufacture, availability and ultimately use. This may reduce the health and social risks and consequences of 4-methylamphetamine. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Finally, control should not inhibit the gathering and dissemination of accurate information on 4-methylamphetamine to users, practitioners and decision-makers.

ANNEX 1

Technical report on 4-methylamphetamine

Dr Paul Dargan, Dr David Wood and Dr István Ujváry

Summary

4-Methylamphetamine is a synthetic phenethylamine stimulant. It is a ring-methylated derivative of amphetamine. Although the drug underwent human clinical trials as an anorectic agent (trade name Aptrol) in the 1950s, it has no current known legitimate industrial, agrochemical, cosmetic, human or veterinary medical use.

4-Methylamphetamine has appeared sporadically on the illicit drug market. The first detection was reported in the United States of America in 1973; subsequently a report of its detection was published in the United Kingdom in 1989. Since the introduction of the European Union early-warning system in 1997, 4-methylamphetamine was first detected ([1]) in Belgium in a seizure made in October 2009, with formal notification to the EMCDDA in December 2009. There have been reports to the EMCDDA and Europol of seizures and collected samples of 4-methylamphetamine in 15 Member States and two other countries that report to the EMCDDA. Most commonly 4-methylamphetamine is found together with amphetamine and caffeine. In only a few cases has 4-methylamphetamine been the only active substance in a seized sample. Generally the analyses have been qualitative and the relative proportion of active ingredients, including 4-methylamphetamine, in the seized products was not estimated. In some of the seizures, the exact position of methyl group in the aromatic ring of the methylamphetamine has not been established and so it is not possible to be definitively certain that the substance contained 4-methylamphetamine and not the 2- or 3-methyl isomer.

Most commonly 4-methylamphetamine is encountered in powder or paste form (commonly white, white-yellow, off-white or yellow). 4-Methylamphetamine has also been detected in liquids and to a lesser degree tablets. There is limited information available that suggests that 4-methylamphetamine is used orally, by nasal insufflation, and by intramuscular injection. The doses reported range from 10–300 mg.

There is limited information available on the prevalence of use of 4-methylamphetamine as there are currently no co-ordinated national or European population surveys on 4-methylamphetamine use. Two small surveys (Hungary and the United Kingdom) have shown self-reported/suspected use of 4-methylamphetamine in a small minority (2.1–5.8 %) of those surveyed. It is possible that in at least some cases, participants reporting the use of 4-methylamphetamine were actually referring to 'methamphetamine' (*N*-methylamphetamine). Since most exposures appear to occur where individuals have attempted to source/use amphetamine ('speed'), there is the potential that use is in fact greater than reported. Additionally, it is likely that the routes of supply of 4-methylamphetamine will be the same as those for amphetamine (e.g. through street level drug dealers).

The only reports of crime and antisocial behaviour related to 4-methylamphetamine use are from Sweden; amphetamine was also involved in all of these cases. There have been reports of seizures of 4-methylamphetamine (together with amphetamine) crossing international borders in the European Union.

Data on the pharmacokinetics of 4-methylamphetamine are limited to one small clinical trial reported in 1950 of six volunteers in which anorectic effects lasted 6–10 hours and significant hypertension lasted 20–30 minutes. In addition, one user reported 'psychedelic effects' with a 'plateau at two hours, and baseline at four hours'.

There have been a number of animal models that have investigated the pharmacodynamics of 4-methylamphetamine; typically these have compared it to amphetamine and/or other ring substituted amphetamines. These studies suggest that 4-methylamphetamine has effects inhibiting re-uptake and stimulating the release of dopamine, serotonin and noradrenaline. Overall it appears to have greater

([1]) '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.).

effects on brain serotonin levels. Importantly, none of these studies involved the co-administration of 4-methylamphetamine with amphetamine and/or caffeine, which is the most prevalent situation observed in the illicit market. As a result there are no data on possible drug interactions.

Animal models suggest that although 4-methylamphetamine has a similar median lethal dose to amphetamine there is variation based on the model used and the route of administration. Human volunteer studies and user reports have shown that 4-methylamphetamine is associated with anorectic effects, hypertension, palpitations, headache, anxiety, insomnia, abdominal pain, hallucinations, paranoia, depression, nausea and vomiting.

A total of 20 non-fatal cases of acute 4-methylamphetamine toxicity or detection of 4-methylamphetamine in drug-related offences have been reported from five Member States. However, limited clinical detail is available in most of these. There is only one published case report of stimulant-like toxicity where 4-methylamphetamine has been identified; however, it is not possible to determine the significance of this as another drug was also detected (4-methylmeth-amphetamine ([2])) and the patient had consumed alcohol.

The first death where 4-methylamphetamine was detected was from the United Kingdom in October 2010. To date, there have been a total of 21 deaths from four Member States (Belgium, Denmark, the Netherlands and the United Kingdom) where 4-methylamphetamine alone or in combination with one or more other substance has been detected in post-mortem samples. Based on the information available it is not possible to determine the significance of the detection of 4-methylamphetamine in relation to the actual cause of death. There have been no reports of 4-methylamphetamine related deaths from other Member States, Croatia, Turkey and Norway.

In conclusion, 4-methylamphetamine is a synthetic phenethylamine stimulant. It is a ring-methylated derivative of amphetamine. There have been seizures from 15 Member States and two other countries that report to the EMCDDA. However, there is limited evidence of widespread use of 4-methylamphetamine within Europe. There have been 21 reported deaths potentially related to 4-methylamphetamine from four Member States. Seizure and exposure data suggests that people are likely to encounter 4-methylamphetamine when attempting to source or use amphetamine ('speed'). The published pharmacodynamic data suggests that 4-methylamphetamine has a similar pattern of toxicity to amphetamine. Overall, the prevalence of use of 4-methylamphetamine and associated toxicity and risks may be greater than is evident from the data that are currently available.

([2]) *N,p*-dimethylamphetamine.

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

4-Methylamphetamine is a synthetic phenethylamine stimulant. It is a ring-methylated derivative of amphetamine. In the 1950s it was studied by Smith, Kline & French Laboratories as a potential anorectic medicine under the trade name Aptrol ([3]).

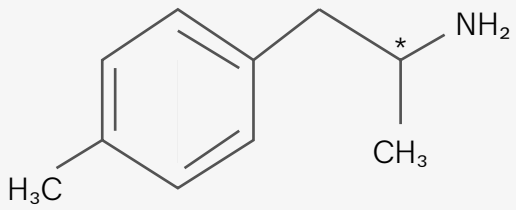
The systematic (International Union of Pure and Applied Chemistry, IUPAC) name of 4-methylamphetamine is 1-(4-methylphenyl)propan-2-amine. Other chemical names encountered in the literature include: 1-(4-methylphenyl)-2-aminopropane; 2-amino-1-(4-methylphenyl)propane or 2-amino-1-(*p*-methylphenyl)-propane; 1-(4-methylphenyl)-2-propylamine; α,4-dimethylbenzeneethaneamine (Chemical Abstract name); 1-(4-methylphenyl)-1-methylethanamine; *p*,α-dimethylphenethylamine; 4-methyl-α-methyl-phenethylamine; *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. The Chemical Abstract Service (CAS) Registry Numbers for 4-methylamphetamine are given in Table 1.

([3]) The trade name Aptrol originally referred to the sulfate salt comprised of two moles of 4-methylamphetamine and one mole of sulfuric acid.

TABLE 1
Chemical Abstract Service (CAS) Registry Numbers for 4-methylamphetamine

CAS Registry Numbers	Variant
64-11-9	unspecified amine
22683-78-9	(±) racemic amine
41632-56-8	HCl salt
878794-34-4	bisulfate
50650-74-3	sulfate as in Aptrol
788775-45-1	(R)-(–) enantiomer amine
81601-14-1	(S)-(+) enantiomer amine
81601-12-9	(R)-(–) enantiomer HCl salt
81601-11-8	(S)-(+) enantiomer HCl salt

FIGURE 1
The molecular structure, formula and weight of 4-methylamphetamine. Asterisk indicates chiral centre



Empirical formula: $C_{10}H_{15}N$

Molecular weights: 149.23 (base); 185.69 (HCl salt); 396.54 ($(C_{10}H_{15}N)_2 \cdot H_2SO_4$ salt, i.e. Aptrol, see below).

4-Methylamphetamine is also known by its code names: pTAP (from *para*-tolylaminopropane); PAL-313; 4-MeA; 4-Me-PIA (thought to stand for 4-methylphenylisopropylamine); and PmeA. The often-used '4-MA' abbreviation should be avoided because this can also denote *para*-methoxyamphetamine (also known as PMA) (Shulgin et al., 2011: 267). It is also important to distinguish 4-methylamphetamine from the substance commonly known as methamphetamine ('meth'), which is correctly called *N*-methylamphetamine.

4-Methylamphetamine contains an asymmetric carbon (Figure 1). Although analytical data are lacking, 4-methylamphetamine sold on the illicit drug market is presumed to be a racemic mixture since the separation of the *R* and *S* enantiomers is costly. Known positional isomers of 4-methylamphetamine are 2-methylamphetamine (also known as 'ortetamine') and 3-methylamphetamine. The *N*-methyl derivative of 4-methylamphetamine as well as several ring and side-chain homologues, including ring-substituted di- and trimethyl, 4-ethyl, 4-propyl and 4-isopropyl, and side-chain homologues have been described (Nabenhauer, 1941; Rosenmund & Karg, 1942; Schnider, 1945; Marsh & Herring, 1950; Holland et al., 1963; Bailey et al., 1974; Bal et al., 1989; Glennon et al., 1992; Arnold et al., 1995; Davis et al., 2012). Notable among these is 3,4-dimethylamphetamine, or 'xylopropamine' (Perhedrin, Esanin), that was studied in the 1950s as an experimental appetite suppressant possessing analgesic and anti-inflammatory properties as well ([4]). The higher homologue, *N*-methyl-1-(4-pentylphenyl)propan-2-amine (amfepentorex) was marketed as an appetite suppressant in France in the 1970s ([5]).

([4]) http://www.chemspider.com/Chemical-Structure.24901
([5]) http://www.chemspider.com/Chemical-Structure.64893

Identification and analytical profile

4-Methylamphetamine gives a positive reaction for the Marquis reagent (orange changing to red); the Mecke reagent (yellow); the Mandelin reagent (brown); there is no colour reaction in the nitroprusside field test (Cordova, 1974; Soine et al., 1992; Bruijns, 2011).

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 (Bailey et al., 1974; Davis et al., 2012). The infrared and nuclear magnetic resonance spectra of these positional isomers also differ (Bailey et al., 1971; Bailey et al., 1974; Bailey & Legault, 1981; Border et al., 1993).

Mass spectral data for 4-methylamphetamine (m/z): 149, 44 (Electron Ionisation / EI spectrum base peak), 150 (M+H+ , base peak), 148 (weak); 133 (Chemical Ionisation / CI spectrum base peak) (Bailey et al., 1974; Saferstein et al., 1974; Brettell, 1983; Westphal et al., 2011; Davis et al., 2012; Strano-Rossi et al., 2012).

Selective liquid chromatography with tandem mass spectrometry (LC-MS/MS) method for the analysis of 4-methylamphetamine in saliva has been developed (Strano-Rossi et al., 2012).

Immunoassay field tests for amphetamines are likely to give a positive reaction with 4-methylamphetamine (Bal et al., 1989), although formal studies have not been published.

Physical description

The free base of 4-methylamphetamine is a nearly colourless liquid with an amine-like odour. Its boiling point is 222–224 °C at atmospheric pressure (Nabenhauer, 1941) and 103–105 °C

at 10 mmHg pressure (Moed et al., 1955) ([6]). It is typically a solid salt form that is present in in seized and collected samples ([7]). The melting point of the water-soluble hydrochloride salt of 4-methylamphetamine is 158–159 ºC (Jacobsen et al., 1938), while the sulfate melts at 263 ºC with decomposition (Cordova, 1974). Both salts are white or lightly coloured crystals. Some websites listed chemical suppliers that could purportedly offer 4-methylamphetamine for sale; however, it is unknown what salt form is being offered.

4-Methylamphetamine has predominately been seized in powder and paste form, but liquids containing the substance have occasionally been encountered. Powders and the paste forms in which 4-methylamphetamine was identified typically also contained amphetamine and caffeine in varying ratios. Tablets and a solution ([8]) of the drug have also been seized; in some cases these also contained amphetamine and/or caffeine. In one case from 2009 the tablets were in commercial packaging that was labelled as an 'ephedrine weight loss' 'dietary supplement' (reported to be sold on the Internet, see Section A1.2.).

Analytical reports of seized, collected and biological samples of 4-methylamphetamine have not indicated the presence of other positional isomers.

As previously noted, no data are available on the enantiomeric composition of 4-methylamphetamine found in seizures, collected samples or biological samples ([9]). Similarly, it is unknown what enantiomeric form is purportedly offered by websites listing chemical suppliers of the drug.

Analytical reference samples of high purity are commercially available ([10]).

([6]) A single paper (Jacobsen et al., 1938) gives a melting point of '90–91 ºC' for the substance they prepared; however, this value refers to the oxime precursor rather than to the amine product.

([7]) For the sake of brevity, the term '4-methylamphetamine' is used throughout the text although it is the hydrochoride or sulfate salt that is seen in seizures and collected samples. For methodological reasons, and because 4-methylamphetamine is frequently mixed with other salt-forming stimulants, the inorganic acid is usually not specified by forensic laboratories that analyse samples.

([8]) Germany reported a seizure of a nasal spray that contained a colourless, clear liquid containing amphetamine, 4-methylamphetamine and caffeine. As hydrochlorides, the amphetamines are readily water-soluble and it is possible that the spray was home-made from a powder or paste.

([9]) Published biological studies, including toxicological ones, have used the racemic mixture. It is not known whether there are differences between the pharmacology of 4-methylamphetamine enantiomers.

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

Methods and chemical precursors used for the manufacture of 4-methylamphetamine

The synthesis of 4-methylamphetamine requires similar equipment and chemical expertise to that needed for the production of other amphetamines. Most published methods for the synthesis of 4-methylamphetamine rely on the reductive amination of 4-methylbenzyl methyl ketone (4-methyl-BMK) ([11]) precursor and use of the Leuckart reaction (Allen & Cantrell, 1989). The 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 produce 4-methyl-amphetamine. 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-methyl-BMK.

Alternative synthetic routes have also been described in the literature. These include using 4-methylbenzaldehyde (p-tolualdehyde) and nitroethane as starting materials (Henry-variant of the Knoevenagel condensation) and reduction of the resultant nitrostyrene with lithium aluminium hydride (LiAlH4) (Bailey et al., 1971; Moed et al., 1955; Muñoz et al., 2011; Davis et al., 2012).

4-Methylamphetamine has also been prepared by alternative synthetic routes (Brown, 1990; Gajda et al., 1997; Wagner et al., 2003). In theory, 4-methylamphetamine could also be synthesised by reductive deoxygenation from the corresponding cathinone derivative (4-methylcathinone) but this route has not been explored ([12]). Methods providing enantiomerically enriched 4-methylamphetamine are also known (Terent'ev & Potapov, 1956; Marco et al., 1987; Chen et al., 2009; Muñoz et al., 2011).

Although it is not clear by what method(s) 4-methyl-amphetamine presently on the illicit market is actually manufactured, the available information suggests that 4-methyl-BMK is one of the precursors. This ketone can be potentially used in general organic synthesis; it appears to be commercially available and is not under international control. As part of the data collection exercise conducted by the EMCDDA for the Joint Report (EMCDDA–Europol, 2012), 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 dozens of email responses from companies

([11]) Other chemical names are 4-methylphenylacetone and 1-(4-methylphenyl) propan-2-one. The CAS Registry Number for this ketone is: 2096-86-8.

([12]) Other synthetic methods can also be envisaged (Soine, 1986).

detailing the price per kilogram, as well as information on payment, shipping, delivery and/or purity. Typically, the price for 4-methyl-BMK ranged from USD 180 to 300 per one kg. The majority of the price quotations appear to originate from companies based in China.

In some of the seized samples, detectable amounts of 4-methyl-BMK and benzyl methyl ketone (BMK) ([13]) have been found. This suggests that 4-methylamphetamine and amphetamine may have been synthesised subsequently in the same (and therefore un-cleaned) reaction vessel or simultaneously in the same batch from the mixture of the respective precursors (see 'typical impurities', below). Studies conducted on two samples containing 4-methylamphetamine seized by police in Ireland (Power et al., 2013) showed that the major impurities were analogous to those found in the manufacture of amphetamine and N-methylamphetamine by the Nagai route using ephedrine and the Leuckart route using BMK.

According to information from Dutch police (Section F), 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.

A recent report (Hao et al., 2007) describing the GC–MS spectrometry-based identification of 4-methylamphetamine in the essential oil of a tropical weed is most probably erroneous ([14]).

Typical impurities encountered in seized samples

In general, the analyses of seized samples containing 4-methylamphetamine revealed great variation in the composition. 4-Methylamphetamine is uncommon as a pure, unmixed material. Of note is that amphetamine is the most common co-occurring substance. It is not clear whether such mixtures of these two amphetamines are produced deliberately or accidentally. In Belgium and the Netherlands it has been hypothesised that the presence of 4-methyl-amphetamine in amphetamine ('speed') samples (Section F) is probably due to a change in the precursors used for the illicit synthesis of amphetamine. For example, it may be the case 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 (Blanckaert, 2012). Impurities characteristic to the Leuckart method have recently been characterized (Błachut et al., 2011; Westphal et al., 2011). The impurity profile of a sample analysed in Germany indicates that amphetamine and 4-methylamphetamine could have been manufactured in the same batch: in addition to the typical 'homodimers' of the two amphetamines, that is *N*,*N*-di-(β-phenylisopropyl)amine (DPIA) and *N*,*N*-di-[β-(4-methylphenyl)isopropyl]amine (D4MPIA), a 'mixed amine' or 'heterodimer' formed either from BMK and 4-methyl-amphetamine or from 4-methyl-BMK and amphetamine during the reaction was also detected. This indicates the simultaneous presence of the two ketone precursors in the reaction mixture (Westphal et al., 2011). The pharmacology and toxicology of D4MPIA dimers are unknown (see Ketema et al., 1990 for information on DPIA).

Caffeine, though not an 'impurity' because it is added intentionally, was found to be present in many seized and collected samples. Some samples have been found to contain ephedrine, MDMA, PMA and/or other phenethylamine derivatives. Caffeine is a typical adulterant observed in amphetamine samples.

For most seizures reported to the EMCDDA and Europol, the ingredient composition has not been quantified. For example, in a multi-kilogram seizure in the United Kingdom, the powder contained amphetamine (as the main identified psychoactive component estimated to be 14 %), 4-methylamphetamine (present in a lower concentration), with a substantial proportion of composition of the powder unspecified (Section C). Adulteration of some products with paracetamol has also been noted (for details on seizures see Section C).

In the early occurrences of 4-methylamphetamine in the United States of America in the 1970s, magnesium sulfate was identified as an adulterant (Cordova, 1974). This inorganic material is unlikely to be detected in forensic laboratories due to the reliance on standard techniques such as Infrared Spectroscopy or Gas Chromatography-Mass Spectrometry.

A1.2. Physical/pharmaceutical form

According to analytical evidence obtained so far, 4-methylamphetamine most frequently occurs in mixtures containing other psychoactive substances in varying ratios (see above). Seizures in Europe indicate that 4-methyl-amphetamine is trafficked on a multi-kilogram scale as powder, paste or liquid (Section C) having various colours (white, off-white, yellow, brown or pink). 4-Methylamphetamine has also been detected in tablet form on the illicit market, as noted in the Netherlands and Czech Republic, and in a commercial 'weight loss' 'dietary supplement' product seized by customs in Norway. In the latter, tablets from a product called 'Green Stinger' were analysed and found to contain a

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

([14]) The paper, referenced in *Chemical Abstracts*, is in Chinese and the abstract does not give sufficient details of the analytical results. Attempts to obtain a full copy of the paper have been unsuccessful so far. Earlier reports on amphetamine-type compounds in plants have not been confirmed.

number of phenethylamines, including 4-methylamphetamine. Germany reported a seizure of a nasal spray containing a colourless solution of 4-methylamphetamine, amphetamine and caffeine.

A1.3. Route of administration and dosage

There are only two user reports relating to the possible use of 4-methylamphetamine. In the first of these, an individual is reported to have used 10–50 mg of product that may have contained '4-methylamphetamine' or '4-methylmeth-amphetamine' ([15]) (Drugs Forum, 2008). No information was provided on the nature of the product or the route of administration. In the second user report to Shulgin et al. (2011: 276) the doses reported were 160 mg for oral use and 80–120 mg for intramuscular injection. There appears to be little or no further information on other popular drug user discussion forums or drug-orientated websites such as Erowid.

As discussed in Section C and Section D, it appears that the majority of exposures to 4-methylamphetamine occur where individuals have attempted to purchase and use amphetamine ('speed') in powder or paste form. It is likely, therefore, that 4-methylamphetamine will be used by similar routes as amphetamine, namely: by oral ingestion, nasal insufflation, intramuscular injection, intravenous injection and rectal insertion. As 4-methylamphetamine is frequently encountered in powder/paste form there is the potential that nasal insufflation is a common route of use. However, it is not possible to be certain of this as there is limited information available from user forums and other sources. Extrapolating from amphetamine use, oral ingestion is likely to be by use of the powder directly (for example by wrapping in cigarette or other paper ('bombing') prior to swallowing), or swallowing tablets or capsules. It is likely that the powder can also be dissolved in water/other liquids. There is one user report of intramuscular injection of 4-methylamphetamine (Shulgin et al., 2011: 276).

Since there is little or no information on Internet drug user discussion forums or in the published scientific and grey literature on the doses of 4-methylamphetamine, it is not possible to determine with certainty those taken by users. Furthermore, there are no data from the non-fatal intoxications and fatal cases related to 4-methylamphetamine (summarised in Section D) on the doses of 4-methyl-amphetamine used. The only information is from two user reports. In the first of these, on a discussion forum, the individual reported using 10–50 mg of a product that was thought to possibly contain 4-methylamphetamine; the route of use was not stated in this report (Drugs Forum, 2008). In the second user report to Shulgin, the doses reported were 160 mg for oral use and 80–120mg for intramuscular injection (Shulgin et al., 2011: 276). Information provided by France that was collected from drug user forums suggested oral doses of 10–300 mg. Overall, since it appears that most use of 4-methylamphetamine occurs when users are attempting to purchase amphetamine ('speed') it is likely that the single use doses of 4-methylamphetamine are similar to those for amphetamine.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacodynamics

There are a number of animal models that have investigated the pharmacodynamic effects of 4-methylamphetamine.

In a series of experiments in different animal models the effects of 4-methylamphetamine were compared to amphetamine (Marsh & Herring, 1950). 4-Methylamphetamine (1:40,000) produced a 30 % decrease in tone in rabbit jejunum compared to a 10 % decrease seen with the same amount of amphetamine. 4-Methylamphetamine produced a similar bronchodilator effect to amphetamine in a guinea pig tracheal chain model: 13 mm decrease in tone for 4-methylamphetamine (1:4000) vs. 15 mm decrease in tone for amphetamine (1:4000). A dose of 15 mg/kg of 4-methylamphetamine was required to produce the same stimulant effects as 2 mg of amphetamine in rats. 4-Methyl-amphetamine was shown to have less anorectic effect than amphetamine in dogs, with an average time following 1 mg/kg administration to begin eating of 65 minutes and 25 minutes respectively, and to complete eating of 30 minutes and 20 minutes respectively. This finding was confirmed in a standardised deprivation-induced fluid consumption test using rats as experimental animals where the most effective anorectic agent in reducing water intake was dextroamphetamine followed by 4-methylamphetamine and fenfluramine (Zabik et al., 1984).

The effects of 4-chloroamphetamine, 4-fluoroamphetamine and 4-methylamphetamine have been compared in a whole rat model at intra-peritoneal doses of 5 mg/kg and 10 mg/kg (Beaton et al., 1968). 4-Methylamphetamine was reported to be the least active of the three compounds tested, with 5 mg/kg causing 'low dose stimulant' and 10 mg/kg causing 'high dose stimulant' effect. All of the rats treated with 4-fluoroamphetamine and 4-chloroamphetamine at a dose of 10 mg/kg died between 6 and 20 hours after administration; although not explicitly stated, it appears that none of the rats treated with 4-methylamphetamine died.

([15]) *N,p*-dimethylamphetamine.

Using a homogenate of whole rabbit adrenal glands the effects of 4-methylamphetamine on phenethanolamine N-methyltransferase (PNMT), responsible for the conversion of noradrenaline into adrenaline, have been studied (Fuller et al., 1971). The inhibition of this enzyme by 4-methylamphetamine was reported to be comparable to that seen with amphetamine and the authors concluded that there was reasonable agreement between the expected inhibition of PNMT compared to that actually seen.

Although about five times less stimulatory in rats *in vivo*, 4-methylamphetamine was more potent than amphetamine in inhibiting rodent brain monoamine oxidase (MAO) enzymes leading to elevated dopamine, and, in particular, serotonin levels both in vitro and in vivo (Fellows & Bernheim, 1950; Ross et al., 1977) ([16]).

In receptor binding studies, 4-methylamphetamine showed low affinity to 5-HT_{1C} and 5-HT_{2A} serotonin receptors (K_i > 10,000 nM for either receptor) while for 2,5-dimethoxy-4-methylamphetamine (DOM) the respective K_i values were 193 and 100 nM indicating that the incorporation of 2- and 5-methoxy groups greatly enhances serotonin receptor-related hallucinogenic activity (Glennon et al., 1992; see also Shannon et al., 1984).

In a mouse model of motor activity, the effects of 4-methylamphetamine were compared to amphetamine and other ring substituted amphetamines (Ögren & Ross, 1977). The drugs were administered intra-peritoneally and motor activity was measured over a 10 minute period half an hour after drug administration. 4-Methylamphetamine increased motor activity: 38 µmol/kg increasing muscle activity by 200 %; the same magnitude of increase in muscle activity was seen with 16 µmol/kg for amphetamine and 24 µmol/kg for both 2- and 3-chloroamphetamine. The authors compared the ED_{200} (the dose required to cause a 200 % increase in motor activity) to previously published EC_{50} for the inhibition of noradrenaline uptake (Ross, 1977). The ratio for 4-methylamphetamine was 0.7, suggesting that the increase in motor activity was predominately due to inhibition of noradrenaline uptake. The authors then compared the ability of drugs to potentiate the 'L-Dopa syndrome' (piloerection, irritability, reactivity, jumping, squeaking and fighting following administration of L-Dopa), where it is known that drugs that inhibit the uptake of noradrenaline potentiate the L-Dopa syndrome. 4-Methylamphetamine was the most potent at potentiating this syndrome (dose giving a +3 response: 7 µmol/kg) compared to amphetamine (dose giving a +3 response: 14 µmol/kg) and the other ring-substituted amphetamines such as 2- and 4-chloroamphetamine (dose giving a +3 response: 24 µmol/kg). Finally the effects of the compounds to potentiate the '5-HTP [5-HT] (5-hydroxytryptophan) syndrome', where administration of 5-HT is associated with head-twitches, tremor and abduction of hind legs, and suggests that the compound inhibits uptake of serotonin (5-HT), were compared. 4-Methylamphetamine was shown to strongly potentiate the 5-HT syndrome, suggesting it has more potent activity in inhibiting 5-HT uptake than *dl*-amphetamine and 2-, 3- and 4-chloroamphetamine.

The effects of 4-methylamphetamine on dopamine, noradrenaline and 5-HT release have been studied on rat caudate homogenates tissue (Wee et al., 2005). The EC_{50} for dopamine and noradrenaline release for 4-methylamphetamine and amphetamine were comparable: [dopamine EC_{50}, 4-methylamphetamine: 44.1 ± 2.6 nM; amphetamine: 8.0 ± 0.43 nM. Noradrenaline EC_{50}, 4-methylamphetamine: 22.2 ± 1.3 nM; amphetamine 7.2 ± 0.44 nM]. However, with respect to 5-HT, 4-methylamphetamine was significantly more potent compared to amphetamine: EC_{50} for 4-methylamphetamine was 53.4 ± 4.1 nM compared to 1756 ± 94 nM for amphetamine. In this study, self-administration of 4-methylamphetamine was compared with other amphetamine analogues including amphetamine, 3-methylamphetamine, 4-fluoroamphetamine and 3-fluoroamphetamine. 4-Methylamphetamine was the least likely of all the compounds to cause self-administration. The authors concluded that there is a decrease in the reinforcing potency and efficacy of a ring-substituted amphetamine when it has greater 5-HT releasing potency compared to dopamine releasing potency.

Rats were treated with 0, 2, 4, 8 and 16 µmol/kg of 4-methylamphetamine, amphetamine and other ring-substituted amphetamines (Wellman et al., 2009). All compounds were noted to reduce food intake in a dose-dependent manner. However, 4-methylamphetamine was noted to cause no significant increase in forward locomotor activity, compared to other analogues including 3-fluoro-amphetamine and 1-naphthyl-aminopropane, which in previous studies have been shown to have potent noradrenaline and dopamine releasing activity but minimal 5-HT releasing activity.

In a squirrel microdialysate model, administration of 4-methylamphetamine was shown to not significantly increase extra-cellular dopamine concentrations compared to placebo and it did not increase behavioural stimulant effects (Kimmel et al., 2009).

The effects of 4-methylamphetamine on extracellular dopamine and 5-HT concentrations were investigated in microdialysis of rat nucleus accumbens (Baumann et al.,

([16]) This finding of MAO inhibition was also predicted by computation analysis as part of the EMCDDA-commissioned study 'Computational analysis on the pharmacology of 4-methylamphetamine' (September 2012), Annex 2 of this publication.

2011). Animals were administered 1 mg/kg 4-methylamphetamine intravenously at time 0, followed by 3 mg/kg intravenously at time 60 minutes. A number of ring-substituted amphetamines were studied including 3-fluoroamphetamine, 4-fluoroamphetamine and 3-methylamphetamine, and it was noted that 4-methylamphetamine was the least potent at increasing extracellular dopamine concentrations. Conversely, 4-methylamphetamine was the most potent at increasing extracellular 5-HT concentrations. 4-Methylamphetamine was shown to be the least potent at increasing locomotor activity, but had comparable effects in terms of stereotypical behaviour effects. The authors concluded that changes in 5-HT concentrations correlated with stereotypical behaviour effects, whereas changes in dopamine concentrations correlated with both stereotypical behaviour and ambulation (locomotor activity). There is the possibility that drugs such as 4-methylamphetamine which, as discussed above, has a predominant effect on 5-HT rather than dopamine, may ameliorate some of the stimulatory and psychoactive effects of amphetamine leading to repeated dosing.

It is worthy of note that no studies involved the co-administration of 4-methylamphetamine and amphetamine, the most prevalent situation observed in the illicit market, therefore there are no data on possible synergistic or other effects. Finally, it must be noted that pharmacological experiments carried out to date used the racemic mixture of 4-methylamphetamine. The pharmacokinetics and pharmacodynamics of the pure *R*- or *S*-stereoisomers may be different and it must be borne in mind that the stereochemistry of seized and collected samples is not known.

There is no published information on the biotransformation (metabolism) of 4-methylamphetamine in animals or humans. It is reasonable to assume, however, that metabolism follows the biochemical pathways established for structurally related substances. These include pyrovalerone derivatives and mephedrone (Michaelis et al., 1970; Cho & Kumagai, 1994; Anderson, 1999; Dalmadi et al., 2003; Springer et al., 2003; Peters et al., 2008; Pedersen et al., 2012).

During the initial oxidative Phase I metabolism, side-chain hydroxylation can occur at the 4-methyl group or at the isopropylamine moieties. The former provides 4-(hydroxymethyl)amphetamine as a postulated metabolite ([17]). The other potential biotransformation step is β-hydroxylation of the isopropylamine chain leading to the known norephedrine homologue (Ueda et al., 1956).

Furthermore, oxidative deamination of 4-methylamphetamine would give rise to the corresponding ketone (4-methyl-BMK).

In subsequent Phase II metabolic steps, excreteable derivatives may be formed by conjugation (e.g., glucuronidation or sulfation) but again such derivatives of the parent drug have not been described so far.

The pharmacological properties of the putative metabolites of 4-methylamphetamine are unknown.

In addition to the potential drug interactions noted earlier (such as with amphetamine and/or caffeine), the overall human pharmacology and toxicity of 4-methylamphetamine may also be influenced by its metabolites. Gender differences and genetic factors may influence the pharmacokinetics of 4-methylamphetamine, in particular its metabolism.

Pharmacokinetics

There are no data available from animal studies in the published or grey literature on the pharmacokinetics of 4-methylamphetamine. One volunteer study in the 1950s investigated the clinical features associated with 4-methylamphetamine use. Here the effects of 4-methylamphetamine and other ring-substituted amphetamines (such as 2- and 3-methylamphetamine) were compared to amphetamine (Marsh & Herring, 1950). Fourteen male volunteers were administered 0.5 mg/kg amphetamine. Of these, six had systolic blood pressure increases of a maximum of 22–28 mmHg. These were then selected for further testing performed at three or four day intervals and administered amphetamine in doses of 0.25, 0.5 and 0.75 mg/kg and the ring-substituted amphetamines given in doses of 0.5, 0.75, 1.0, 1.5 and 2.0 mg/kg. 4-Methylamphetamine induced anorectic effects lasted 6–10 hours after 1.5 mg/kg 4-methylamphetamine and severe hypertension lasted 20–30 minutes after 2.0 mg/kg of 4-methylamphetamine (Marsh & Herring, 1950). There is limited information available from user reports or Internet drug user discussion forums to be able to determine pharmacokinetic parameters such as time to onset of desired / adverse effects or duration of action of 4-methylamphetamine. The only information is provided in a personal communication to Shulgin et al., in which a user reported 'psychedelic effects' with a 'plateau at two hours, and baseline at four hours' after self-reported use of oral (160 mg) and intramuscular (80–120 mg) 4-methylamphetamine (Shulgin et al., 2011: 276).

([17]) For amphetamine, hydroxylation of the aromatic ring at position 4 is possible and the resulting 4-hydroxyamphetamine (paredrine) is pharmacologically active (adrenergic). Such catecholamine-like 4-hydroxymethylated structural moietes can be found in adrenergic antiasthmatic bronchodilators, including albuterol.

A3. Psychological and behavioural effects

There are no published formal studies assessing the psychological and/or behavioural effects of 4-methylamphetamine in humans.

In model experiments with cats, rabbits and rats, the pharmacological spectrum of 4-methylamphetamine was more LSD-like than that of amphetamine, though it was much less active than 2,5-dimethoxy-4-methylamphetamine (DOM), the prototypical hallucinogen used in the study (Aldous et al., 1974).

The user report from the Internet discussion forum noted in Section A1.3 suggests that the undesired psychological and behavioural effects related to 4-methylamphetamine use included 'headache, nervousness and stimulation resembling ephedra' (Drugs Forum, 2008). There is no information as to whether there was concomitant use of other substances that could have contributed to the unwanted effects described. Additionally, since this is a user report, there is no analytical confirmation that the individual had indeed used 4-methylamphetamine; the report suggests that it may have been either '4-methylamphetamine' or '4-methylmethamphetamine'.

A4. Legitimate uses of the product

4-Methylamphetamine is used as an analytical reference standard and in scientific research (which is often in combination with amphetamine and related compounds, many of which are under international control). There are no other indications that 4-methylamphetamine may be used for any other legitimate purposes. There are no known uses of 4-methylamphetamine as a component in industrial, cosmetic or agricultural products.

Racemic 4-methylamphetamine, known by its trade name Aptrol, underwent human clinical trials as an anorectic agent in the 1950s (Section D). 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.

Claims have been made in the patent literature on the use of 4-methylamphetamine as a potential medicine. These include the treatment of stimulant addiction, as an analgesic, and as an antiparkinson agent (Caron et al., 2007). Claims have also been made for its use as an intermediate in the synthesis of potential medicines (Ferris, 1986). 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 currently used in the manufacture of any medicinal product in the European Union. However, in the absence of a European Union database on the synthetic routes of all medicinal products this information cannot be verified. There is no marketing authorisation (existing, ongoing or suspended) for 4-methylamphetamine neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency (EMCDDA–Europol, 2012).

As discussed, 4-methylamphetamine has recently been used as a pharmacological tool to study *in vitro* and in animal models the relationship between the monoamine neurotransmitter-releasing properties and the behavioural effects of amphetamine-type stimulants (Wee et al., 2005; Rothman et al., 2006; Wellman et al., 2009). In a recent experiment with squirrel monkeys, 4-methylamphetamine failed to elicit behavioural-stimulant effects and it was suggested by the authors that it may have potential in the treatment of cocaine dependence (Kimmel et al., 2009).

Section B. Dependence and abuse potential

B1. Animal *in vivo* and *in vitro* data

A study by Wee et al. (2005) compared self-administration of 4-methylamphetamine with other amphetamine analogues including amphetamine, 3-methylamphetamine, 4-fluoroamphetamine and 3-fluoroamphetamine. 4-Methylamphetamine was the least likely of all the compounds to cause self-administration in both a fixed-ratio schedule and a progressive ratio schedule, as shown in Figures 2 and 3.

FIGURE 2

Self-administration under a fixed-ratio schedule (Wee et al., 2005). Key: PAL-353: 3-fluoroamphetamine; PAL-303: 4-fluoroamphetamine; PAL-314: 3-methylamphetamine; PAL-313: 4-methylamphetamine

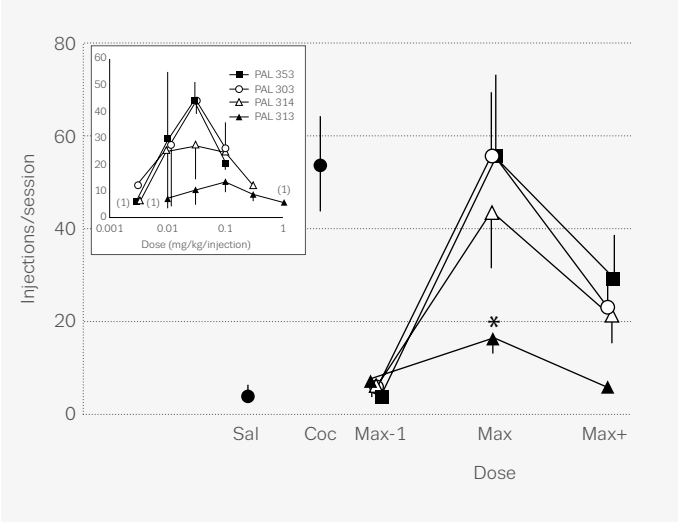
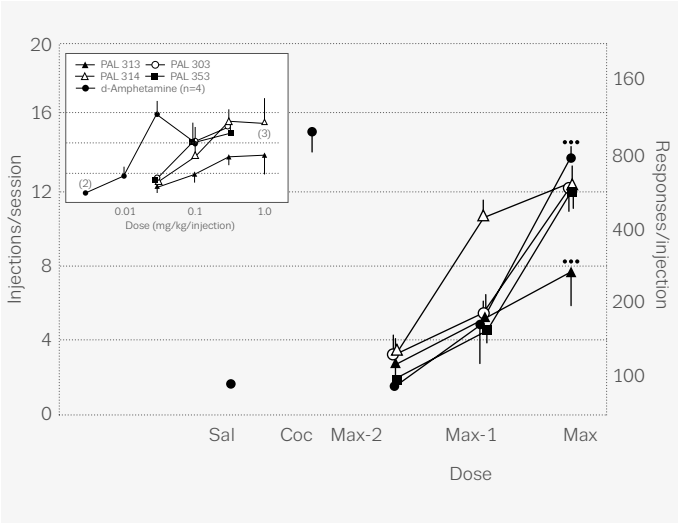


FIGURE 3

Self-administration under a progressive-ratio schedule (Wee et al., 2005). Key: PAL-353: 3-fluoroamphetamine; PAL-303: 4-fluoroamphetamine; PAL-314: 3-methylamphetamine; PAL-313: 4-methylamphetamine



B2. Human data

There are no user reports or published cases in the scientific or grey literature describing the dependence or abuse potential for 4-methylamphetamine. Additionally, there have been no formal studies investigating the dependence and/or abuse potential of 4-methylamphetamine in humans. We are not aware of any reports from local, regional or national drug treatment agencies relating to 4-methylamphetamine dependence. It is possible that this is due to the fact that exposure to 4-methylamphetamine relates to individuals sourcing amphetamine ('speed') rather than 4-methylamphetamine itself. Therefore, users are unlikely to report that the primary (or secondary) drug associated with their dependency is 4-methylamphetamine.

Section C. Prevalence of use

In a historical context, 4-methylamphetamine has appeared sporadically on the illicit drug market. Its appearance was reported first from the United States of America in 1973 (Keaton, 1973; Cordova, 1974) and later it was also detected in the United Kingdom (Bal et al., 1989). Internet searches for '4-methylamphetamine' found that the use and effects of the substance have been discussed by drug users from mid-2008, who note that it was 'known in Russia and Ukraine' (Bluelight, 2008, 2009). Since the introduction of the European Union early-warning system in 1997, 4-methylamphetamine was first detected in Belgium in 2009, with formal notification to the EMCDDA on the 14 December 2009. There have been reports to the EMCDDA and Europol of seizures and collected samples of 4-methylamphetamine in 15 Member States as well as Croatia and Norway. In some of the seizures, the exact position of methyl group on the aromatic ring has not been identified and so it is not possible to be definitively certain that the substance was 4-methylamphetamine.

Most commonly in seizures and collected samples, 4-methylamphetamine has been found together with amphetamine and caffeine (Table 2). 4-Methylamphetamine has been the only active substance in a seized sample in only a few cases. This has been the case in some of the samples seized in Belgium, Croatia, Denmark, France, Germany, Ireland, the Netherlands and Sweden. Generally the analyses have been qualitative and so the amount of 4-methyl-amphetamine detected has not been reported and it is not possible to state the relative proportion of active ingredients in the seized products. In cases where the amount of 4-methylamphetamine present is reported this has varied from a trace or minor component to a small number of reports in which 4-methylamphetamine is reported as a larger or main component of the mixture.

Seizures have varied in size from as small as 0.02 g (Germany in 2011) to 147 kg (France in 2012). Most commonly, these seizures have involved 4-methylamphetamine in powder or paste form (commonly white, white-yellow, off-white or yellow); there have also been reports of 4-methylamphetamine being seized in liquid (France, Germany, Sweden) and tablet (the Netherlands and Norway) form.

TABLE 2

Details of the seizures and collected samples of 4-methylamphetamine reported to the EMCDDA and Europol. In a small number of cases the date listed may refer to the date the information was reported to EMCDDA

Year/ordered by country	Amount and details of the seizure/collected sample
Austria	
2010	One yellow powder sample seized by police weighing approximately 2 kg, also containing amphetamine.
2011	Four yellow powder samples seized by police: 260 g, 50 g, 49 g and 4 g, all containing amphetamine.
2012	Four collected samples from a 'party' analysed on 14/04/2012. All samples had been sold as 'speed': one white paste-like powder (0.060 g) containing 4-methylamphetamine (24 mg/g), amphetamine (95 mg/g), ephedrine (16 mg/g) and caffeine (65 mg/g); one white powder 'self-made' (1.126 g) containing 4-methylamphetamine (16 mg/g), amphetamine (208 mg/g), caffeine (542 mg/g); one white powder (0.03 g) containing 4-methylamphetamine (4 mg/g), amphetamine (73 mg/g) and caffeine (145 mg/g); and one paste-like white powder (0.103 g) containing 4-methylamphetamine (19 mg/g), amphetamine (69 mg/g), ephedrine (27 mg/g) and caffeine (66 mg/g).
2012	Two collected samples from a 'party' analysed on 25/05/2012. All samples had been sold as 'speed': one white powder (0.69 g), containing 4-methylamphetamine (19 mg/g), amphetamine (67 mg/g) and caffeine (62 mg/g); and one white powder (0.19 g) containing 4-methylamphetamine (8 mg/g), amphetamine (34 mg/g), 4-methylethcathinone (40 mg/g), caffeine (384 mg/g), paracetamol (59 mg/g) and an unknown substance.
2012	A further 13 samples (weights unknown) analysed between July and September 2012 containing 4-methylamphetamine (trace to 231 mg/g) and amphetamine (40–327 mg/g). One of these samples contained 4-methylamphetamine (231 mg/g) and amphetamine (647 mg/g).
2012	Several small seizures made by police. All weighed less than 1 g and contained 4-methylamphetamine, amphetamine and caffeine.
Belgium	
2009	16 bags, each containing a piece of yellow paste in aluminium foil. Of these, nine bags contained approximately 5 g of paste, one bag 39 g, six bags 70–80 g. Also contained 4-methyl BMK and 'other by products'.
2010	Two seizures of 1.81 g powder also containing amphetamine and caffeine.
2010	One seizure of 137 g paste also containing 4-methyl-BMK and caffeine.
2011	One report of powder found on a fatality containing 4-methylamphetamine (56 %), amphetamine (14 %) and caffeine (13 %).
2011	One report of powder found on a fatality also containing amphetamine and caffeine.
2011	One report of powder found on an intoxicated patient containing 4-methylamphetamine (64 %), amphetamine (16 %) and caffeine (15 %); purchased as 'Special K' (street name for ketamine).
2011	Three powder samples for which two the purity is known (56 % and 64 %) also containing amphetamine and caffeine.
2011	One seizure containing: one plastic bag with 1.8 g of white-yellow powder; a brown leather 'etui' with six plastic bags: two containing white powder (0.5 g, 0.8 g); three containing yellow powder (0.7 g, 2.5 g, 1.3 g); and one containing white-yellow powder 1.8 g.
2011	Two powder seizures (unknown amount) also containing amphetamine and caffeine.
2011	Two seizures of paste also containing caffeine and amphetamine: one seizure weighed 10.2 g; the second seizure was comprised of sachets weighing 10.5 g, 34.4 g and 100.5 g and bags ranging from 954.7 g to 990.5 g.
2011	Two seizures also containing caffeine, amphetamine, cannabinol and THC.
2012	One report of yellow-white powder in the possession of a patient (fatal case) that contained 4-methylamphetamine and amphetamine.
2012	One report of a powder in the possession of a patient (fatal case) that contained 4-methylamphetamine, amphetamine, caffeine and diphenylisopropylamine (DPIA).
2012	One seizure of 82 g of yellow paste containing 4-methylamphetamine (21 %) also containing amphetamine (13 %) and caffeine (16 %).
2012	One 'pacson' containing 1.4 g of yellow powder containing 4-methylamphetamine HCl (37 %) also containing amphetamine sulphate (23 %).
2012	In June, a syringe was analysed containing 4-methylamphetamine, amphetamine and caffeine (not quantified).
2012	A seizure of 179.6 g of powder was made by federal police services in June. Contents: caffeine (35 %), amphetamine-sulphate (21 %), 4-methylamphetamine (<1 %).
Bulgaria	
	No reports.
Cyprus	
	No reports.

Year/ordered by country	Amount and details of the seizure/collected sample
Czech Republic	
2012	One seizure in the second half of 2012 of several pieces of tablets. MDMA was the major component and 4-methylamphetamine was present in a small amount. Analytical data are not yet available.
Denmark	
2010	One seizure of 1 g of white powder.
Estonia	
	No reports.
Finland	
2011	32 seizures of powder totalling 1070 g, also containing amphetamine. Earliest case was seized 18 April 2011.
France	
2009	One sample of a paste with a 'strong smell', also containing amphetamine, collected from a user.
2011	9 kg of liquid also containing amphetamine.
2011	81.7 kg of a white paste also containing amphetamine (19 %) and caffeine.
2012	147 kg of a paste (undefined colour) also containing amphetamine and caffeine; this is the largest seizure reported to the EMCDDA and Europol.
2012	42 kg of paste also containing amphetamine and caffeine.
No date	Unknown quantity of yellow powder containing 4-methylamphetamine.
Germany	
2010	938 g of white 'amphetamine-like' powder.
2010	3.29 g of a brown powder also containing amphetamine and caffeine.
2010	45.4 g also containing amphetamine and caffeine.
2010	744.5 g of a colourless moist substance also containing caffeine.
2010	0.342 g and 0.194 g of mixtures also containing amphetamine and caffeine.
2010	Four samples containing methylamphetamine (position of methyl group not identified) and other undefined active ingredients.
2010	652 g of a white moist cluster also containing amphetamine.
2011	8.7 g of a brown-yellow coloured substance also containing amphetamine and caffeine (exact position of methyl group in the methylamphetamine not identified).
2011	Seven samples totalling 240.4 g also containing amphetamine and caffeine.
2011	948.46 g of a mixture also containing amphetamine and caffeine (exact position of methyl group in the methylamphetamine not identified).
2011	Seizure of white powder (weight unknown) containing 4-methylamphetamine.
2011	Amphetamine samples (amount unknown) containing traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	10 kg of white powder also containing amphetamine, caffeine and traces of 4-methyl-BMK.
2011	Amphetamine samples (amount unknown) containing traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	Amphetamine samples (amount unknown) containing traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	27 g of amphetamine with traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	1007.9 g amphetamine found to contain a small amount of 4-methylamphetamine.
2011	Amphetamine samples (amount unknown) containing traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	77 g of amphetamine with traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	255.2 g of a mixture also containing amphetamine and caffeine.
2011	Two seizures totalling 2.49 g of a beige substance also containing amphetamine.
2011	1.46 g of a yellow substance containing amphetamine and caffeine.

Year/ordered by country	Amount and details of the seizure/collected sample
2011	Nasal spray with colourless liquid also containing amphetamine and caffeine.
2011	Amphetamine samples (amount unknown) containing traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	Approximately 260 g of white substance filled into small plastic bags for sale also containing amphetamine, caffeine and lactose.
2011	4.5 g of amphetamine with traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	6.23 g of a grey substance also containing amphetamine.
2011	1.1 g of a yellow substance also containing amphetamine and caffeine.
2011	Amphetamine samples (amount unknown) containing traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	77.6 g of a mixture also containing amphetamine and caffeine. The 'relation' between 4-methylamphetamine and amphetamine 'was about 50 to 50'.
2011	554 g of amphetamine with traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	Two seizures of 318.3 g also containing amphetamine and caffeine.
2011	22.9 g also containing amphetamine and caffeine.
2011	16 shrink-wrapped plastic bags each containing 1 kg of white substance (16 kg in total). All contained amphetamine and caffeine; an unknown number also contained 4-methylamphetamine.
2011	257.8 g also containing amphetamine, methoxyamphetamine and caffeine (exact position of methyl group in the methylamphetamine not identified).
2011	0.54 g of white substance also containing amphetamine and caffeine.
2011	Amphetamine samples (amount unknown) containing traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2011	1.9 g of white substance also containing amphetamine and caffeine.
2011	8.8 g also containing amphetamine and caffeine (exact position of methyl group in the methylamphetamine not identified).
2011	0.6 g of white substance also containing caffeine and amphetamine.
2011	0.02 g of white substance also containing amphetamine, di-(beta-phenylisopropyl-)amine and caffeine.
2011	91 g of amphetamine with 'smaller part' of 4-methylamphetamine and caffeine.
2011	One plastic bag labelled '2.0g PEP' and two bags labelled '1.2g PEP' also containing caffeine (exact position of methyl group in the methylamphetamine not identified).
2012	Unknown amount of white powder also containing amphetamine, di-(beta-phenylisopropyl-)amine, caffeine, cocaine and THC.
2012	Analysis of forensic checks of amphetamine samples, amount unknown, contained traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2012	2.22 kg of a mixture also containing amphetamine and 4-methoxyamphetamine.
2012	19.8 g of a mixture also containing amphetamine and caffeine.
2012	Approximately 90 g of 4-methylamphetamine (no further details available).
2012	19.7 g of 4-methylamphetamine 'laced' with caffeine and lactose.
2012	22.9 g of a mixture also containing amphetamine, 4-methoxyamphetamine and caffeine.
2012	41 g of a mixture also containing MDMA, amphetamine, 4-methoxyamphetamine and caffeine.
2012	51.63 g of white powder also containing amphetamine and caffeine (exact position of methyl group in the methylamphetamine not identified).
2012	Analysis of an amphetamine sample (amount unknown) contained traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2012	76.4 g also containing amphetamine and caffeine.
2012	40 g of amphetamine with traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2012	21.2 g of a mixture also containing amphetamine and caffeine (exact position of methyl group in the methylamphetamine not identified).
2012	0.15 g of a mixture also containing amphetamine and caffeine.
2012	42.5 g of 4-methylamphetamine 'laced' with caffeine.
2012	96.9 g of a mixture also containing amphetamine and caffeine.

Year/ordered by country	Amount and details of the seizure/collected sample
2012	Analysis of an amphetamine sample (amount unknown) contained traces of methylamphetamine (exact position of methyl group in the methylamphetamine not identified).
2012	133.8 g of a white powder also containing caffeine.
Greece	
	No reports.
Hungary	
2010	Two seizures: one of 21 g yellow powder containing 4-methylamphetamine; one seizure of nine packages, with a total of 1768 g of yellow powder also containing amphetamine (2–3 %) and caffeine. 4-Methylamphetamine was present in a similar concentration to amphetamine.
Ireland	
2012	11.9 g of a yellow-orange waxy powder/paste.
2012	5.61 g of a white powder also containing amphetamine.
2012	487.807 g powder in 18 packs.
Italy	
	No reports.
Latvia	
	No reports.
Lithuania	
	No reports.
Luxembourg	
2010	One seizure of 6 g of powder. No other psychoactive ingredients were detected.
Malta	
	No reports.
Netherlands	
2009	Four collected samples of powders (amount not stated) analysed by the Drugs Informatie en Monitoring Systeem (DIMS) project.
2010	Four seizures of powder (amount not stated).
2010	1006 collected 'speed' samples (powders) analysed, 10 % contained 4-methylamphetamine (DIMS).
2011	946 collected 'speed' samples (powders) analysed, 9 % contained 4-methylamphetamine (DIMS).
2011	Out of 1,560 amphetamine seizures (powders) analysed: 81 samples containing amphetamine in combination with 4-methylamphetamine and 27 samples contained 4-methylamphetamine only. 37 samples contained a little amount of 4-methylamphetamine. This includes 24 seizures of powder that weighed 6.3 kg.
2012	Up to May, of 461 amphetamine seizures (powders) analysed, 30 samples contained amphetamine in combination with a substantial amount of 4-methylamphetamine and 11 samples contained 4-methylamphetamine only. 44 amphetamine samples contained minimal amounts of 4-methylamphetamine.
2012	Up to June, of 685 collected 'speed' samples analysed (amount and type of samples not stated), 17 % contained 4-methylamphetamine; also six tablets containing both amphetamine and 4-methylamphetamine (DIMS).
Poland	
2011	Seizure of four powders each weighing 2 g (two light yellow and two light pink); contained predominantly amphetamine sulfate (83–86 %) with a 'small amount' of 4-methylamphetamine and DPIA.
Portugal	
	No reports.
Romania	
	No reports.
Slovakia	
	No reports.
Slovenia	
	No reports.

Year/ordered by country	Amount and details of the seizure/collected sample
Spain	
2012	Three collected samples of a powder (unknown amount) also containing amphetamine, caffeine, di-(β-phenylisopropyl)-amine, N-formylamphetamine, N-(-phenylisopropyl)benzaldimine.
Sweden	
2009	One seizure of 7.28 g of yellow powder.
2010	4-Methylamphetamine was found in 198 cases together with already controlled substances (e.g. amphetamine).
2011	4-Methylamphetamine was found in 256 cases and 17 liquid samples together with already controlled substances (e.g. amphetamine).
United Kingdom	
2010	One seizure of 0.19 g white powder also containing amphetamine and caffeine.
2011	92.8 g compressed damp-off white powder also containing caffeine.
2012	967.7 g damp off-white powder also containing amphetamine and caffeine (analysed by GC-MS and so position of methyl group not confirmed).
2012	6.288 g damp white powder also containing amphetamine and caffeine (analysed by GC-MS and so position of methyl group not confirmed).
2012	Plastic package containing 1.846 g white powder also containing amphetamine and caffeine (analysed by GC-MS and so position of methyl group not confirmed).
2012	8.67 g white powder also containing amphetamine (analysed by GC-MS and so position of methyl group not confirmed).
2012	36.72 g white powder also containing amphetamine (analysed by GC-MS and so position of methyl group not confirmed).
2012	0.847 g white powder also containing amphetamine and caffeine (analysed by GC-MS and so position of methyl group not confirmed).
2012	13.09 g white powder also containing amphetamine and caffeine (analysed by GC-MS and so position of methyl group not confirmed).
2012	3 g white powder also containing amphetamine and caffeine (analysed by GC-MS and so position of methyl group not confirmed).
2012	5.1 g white powder also containing amphetamine, paracetamol and caffeine (analysed by GC-MS and so position of methyl group not confirmed).
2012	Four seizures of powder (0.573 g, 0.321 g, 0.359 g, 98.1 g) also containing amphetamine and caffeine (4-methylamphetamine identified by GC-MS by comparison to a standard).
2012	1.63 g powder also containing amphetamine and caffeine (4-methylamphetamine identified by GC-MS by comparison to a standard).
2012	72 g compressed off-white damp substance also containing amphetamine (< 1 %).
2012	Approximately 34 kg of powder also containing amphetamine (14 %). Although the concentration of 4-methylamphetamine was not determined, it was known to be lower than the amphetamine present.
Croatia	
2010	In 2010 there were only ten cases of seizures where 4-methylamphetamine was present. Total weight of these seized drugs was 268.01 g.
2011	Out of 6,324 individual seizures during 2011, traces of 4-methylamphetamine were found in 18 cases, or 0.28 % of total number of seizures. Total weight of seized drugs which contained traces of 4-methylamphetamine was 251.07 g.
2012	19 cases (total amount 747.62 g) of 4-methylamphetamine mixed with amphetamine.
2012	In two separate cases (total amount 4.12 g), 4-methylamphetamine concentrations were 2.7 % and 2.9 %. Powders also contained amphetamine.
Turkey	
	No reports.
Norway	
2009	One seizure of 120 tablets in a commercial product called 'Green Stinger'. [A product bearing this name is sold on the internet as an 'ephedrine weight-loss product' (4-methylamphetamine is not listed as an ingredient on this product).]. Analysis revealed that no ephedrine was present, with MS-data indicating a mix of several compounds: 4-methylamphetamine, 1-phenylethylamine, 2-phenylethylamine, β-methyl-phenethylamine, N,N-dimethyl-phenethylamine, N-benzyl-1-phenylethylamine, caffeine and yohimbine.
Undated	Two seizures of 0.345 g and 0.136 g of powder also containing amphetamine.

There are currently no coordinated national or European general population surveys on 4-methylamphetamine use. Further, the European school survey project on alcohol and other drugs (ESPAD) and other school/college/university surveys have not investigated or reported on 4-methylamphetamine use. One online survey conducted by DAATH (the online discussion forum of the Hungarian Psychedelic Community) and the Hungarian national focal point was conducted 15–25 June 2012 on the forum daath.hu (EMCDDA–Europol, 2012). Of the 194 individuals who completed the survey, 4 (2.1 %) thought that they had used 4-methylamphetamine. However the street names provided in two of these cases, 'formek' (generally associated with 4-methylethcathinone) and 'piko' (generally associated with methamphetamine), suggest that this may be an overestimate. In one survey using a similar methodology to a previous published study (Measham et al., 2011), 330 individuals attending gay-friendly nightclubs in South London, United Kingdom in July 2012 were asked about their knowledge and frequency of use of 4-methylamphetamine and amphetamine ('speed') as a comparator. This was part of a larger questionnaire survey on the self-reported use of a number of other recreational drugs and new psychoactive substances. Of these, 16.2 % had heard of 4-methylamphetamine (97 % had heard of amphetamine), 5.8 % reported having ever used it (43.9 % had used amphetamine), 4.0 % had used it in the last year (16.5 % had used amphetamine) (personal communication from Fiona Measham, David Wood, Paul Dargan). It is possible that in at least some cases, participants reporting the use of 4-methylamphetamine were actually referring to 'methamphetamine' (*N*-methylamphetamine).

Given that the available data indicate that 4-methylamphetamine is usually sold as amphetamine ('speed') it should be noted that EMCDDA drug prevalence estimates suggest that about 13 million Europeans have tried amphetamines (a generic term that includes both amphetamine and methamphetamine — and it is important to note that there have been no indications that 4-methylamphetamine has been sold as 'methamphetamine'), and about 2 million have used the drug during the last year. Among young adults (aged 15 to 34), lifetime prevalence of amphetamines use varies considerably between countries, from 0.1 % to 12.9 %, with a weighted European average of 5.5 %. Last year use of amphetamines in this age group ranges from 0 % to 2.5 %, with most countries reporting prevalence levels of 0.5 % to 2.0 %. It is estimated that about 1.5 million (1.2 %) young Europeans have used amphetamines during the last year. Levels of last year use of amphetamines are higher in surveys among young people linked with dance-music or nightlife settings, with results from 2010 studies in the Czech Republic, the Netherlands and the United Kingdom ranging from 8 % to 27 %.

Among 15- to 16-year-old school students, lifetime prevalence of amphetamines use ranged from 1 % to 7 % in the 24 Member States, Croatia and Norway with ESPAD surveys in 2011, although only Belgium, Bulgaria and Hungary reported prevalence levels of more than 4 % (60). The Spanish national school survey reports 1 %.

Between 2005 and 2010, last year amphetamines use has remained relatively low and stable among the general population in most European countries, with prevalence levels of less than 3 % in all reporting countries. During this period an increase was reported by only one country, Bulgaria, which observed an increase of one percentage point in last year prevalence of amphetamines use among young adults. ESPAD school surveys conducted in 2011 suggest, overall, little change in the levels of experimentation with amphetamines among students aged 15 to 16 (EMCDDA, 2012).

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

The reported acute toxicity data for 4-methylamphetamine (and comparative data for amphetamine) expressed as median lethal dose (LD_{50}, mg/kg) in mouse models are shown in Table 3.

Based on the LD_{50} data, the acute toxicity of 4-methylamphetamine appears to be similar to amphetamine in the mouse model. Studies by Riva et al. (1969) indicate that crowding potentiates the lethality of both amphetamine and 4-methylamphetamine (the phenomenon of 'amphetamine aggregation-toxicity' has been previously noted for these type of compounds).

Additional toxicity data were reported by Fellows and Bernheim (1950). The oral LD_{50} value of 4-methylamphetamine ([18]) for rats was found to be 150 mg/kg.

There is no information on the pharmacology or toxicology of dimer synthetic impurities detected in 4-methylamphetamine samples (Westphal et al., 2011) ([19]).

([18]) The authors did not specify what kind of 'neutral salt' had been used.
([19]) The animal pharmacology and toxicology of a dimer impurity (DPIA) occurring in illicit amphetamine samples has been studied. See, for example, Ketema et al., 1990.

TABLE 3

Acute animal toxicity data for 4-methylamphetamine (and comparative data for amphetamine) expressed as median lethal dose (LD_{50}, mg/kg). Key: a: sulphate salt; b: hydrochloride salt

Model	LD_{50} 4-methylamphetamine	LD_{50} amphetamine	Reference
Mouse, intraperitoneal administration, kept in isolation	136[a]	101[a]	Marsh & Herring, 1950
Mouse, intraperitoneal administration, kept in groups of five	12[b]	40[b]	Benington et al., 1965
Mouse, intravenous administration	31.0	12.5	Haas & Forth 1956
Mouse, subcutaneous administration	76	47	Haas & Forth 1956
Mouse, oral administration	115	45	Haas & Forth 1956
Mouse, subcutaneous administration, kept in isolation	160[b]	205[b]	Riva et al., 1969
Mouse, subcutaneous administration, kept in groups of ten	35[b]	15.5[b]	Riva et al., 1969

The majority of forensic reports, including post-mortem analyses, note the co-presence of caffeine in seizures, collected and biological samples. It is important to note that adverse drug interactions, such as the enhancement of the acute toxicity of 4-methylamphetamine (or from amphetamine that was co-present in many samples), should not be underestimated. The toxicity-potentiating effect of caffeine when combined with stimulants, including amphetamine, has been documented (Derlet et al., 1992; Sinchai et al., 2011). In one study, while caffeine pre-treatment potentiated the anorectic activity of 4-methylamphetamine, no such effect was seen for amphetamine (Cox & Maickel, 1976). This observation suggests the existence of drug interactions for caffeine and 4-methylamphetamine.

D1.2. Human data

One volunteer study in the 1950s investigated the clinical features associated with 4-methylamphetamine use. Here the effects of 4-methylamphetamine and other ring-substituted amphetamines (such as 2- and 3-methylamphetamine) were compared to amphetamine (Marsh & Herring, 1950). Fourteen male volunteers were administered 0.5 mg/kg amphetamine. Of these, six had systolic blood pressure increases of a maximum of 22–28 mmHg. These were then selected for further testing performed at three or four day intervals and administered amphetamine in doses of 0.25, 0.5 and 0.75 mg/kg and the ring-substituted amphetamines given in doses of 0.5, 0.75, 1.0, 1.5 and 2.0 mg/kg. Anorectic effects, along with physiological effects, were recorded following administration. At doses of 1 mg/kg, 4-methylamphetamine was noted to have minimal effects on blood pressure (systolic increase of 14 mmHg, diastolic increase of 4 mmHg) and did not change heart rate, and volunteers reported that they were 'not hungry'. At 1.5 mg/kg, nausea and perspiration were present and the anorexia persisted for six to ten hours; there was an average increase in systolic blood pressure of 18 mmHg and diastolic of 16 mmHg. A dose of 2.0 mg/kg resulted in 'severe and prolonged anorexia' and volunteers 'complained bitterly of gastric distress with much salivation, expectoration and coughing, terminating in copious vomiting of mucus secretions'. There was a greater increase in blood pressure (systolic increase of 50 mmHg and diastolic of 34 mmHg); these persisted for 20–30 minutes, before falling to approximately 20 mmHg above baseline. The authors felt that it was not possible to compare the effects of 4-methylamphetamine directly to the effects of amphetamine. However, they stated that a dose of 1 mg/kg 4-methylamphetamine produced a blood pressure rise about equal to a dose of 0.25 mg/kg amphetamine.

Shulgin and Shulgin (1997) provide some limited data on experiments in humans looking at all three ring-substituted mono-methylamphetamine isomers (2-, 3- and 4-methyl-amphetamine). No information is provided on the methodology of the experiments or the number of volunteers. They describe 2- and 3-methylamphetamine as weak anorexics that at oral doses of up to 150 mg cause signs of stimulation (talkativeness) and loss of appetite. 4-Methylamphetamine at an oral dose of 75 mg was said to cause 'clear signs of adrenergic stimulation' (no details are given), and at an oral dose of 150 mg they note 'signs of mild toxicity such as salivation, coughing and vomiting'. In a self-experiment, 'psychedelic activity' was reported at 160 mg oral dose and at 80–120 mg by intramuscular injection, with a 'plateau at two hours, and baseline at four hours' (Shulgin et al., 2011: 276).

There has been one reported clinical trial of 4-methyl-amphetamine as an anorectic agent (Aptrol) in weight reduction (Gelvin & McGavack, 1952). A total of 65 individuals were recruited for the study, with each individual acting as their own control, comparing clinical and adverse effects during the treatment and placebo arms. In total 48 were

administered 4-methylamphetamine and then placebo, 14 only 4-methylamphetamine and 11 only placebo. In addition, individuals were placed on a strict 1,000 calories per day diet. Treatment was initiated at 25 mg three times a day, and increased if tolerated to 50 mg three times a day. Weight loss during 4-amphetamine phase was 0.8 pounds per week compared to 0.2 pounds per week with placebo. The authors reported that there was no significant difference between 4-methylamphetamine and placebo in terms of effects on blood pressure, heart rate and the 'majority of unwanted effects'. There was no difference in the frequency of unwanted effects such as 'weakness', 'giddiness', 'faintness', nausea and vomiting associated with 4-methylamphetamine administration compared to placebo. There were no changes in haemoglobin, total leucocyte count or polymorphonuclear lymphocyte count with 4-methylamphetamine administration compared to placebo. Unwanted effects that appeared only to be reported during 4-methylamphetamine use were headache, pruritis and palpitations (all of these occurred in 3 % of 4-methylamphetamine treated individuals).

D1.2.1. User reports

There are limited user reports discussing 4-methyl-amphetamine. It is likely that this is because 4-methyl-amphetamine is generally sold as amphetamine ('speed') and therefore users are unaware that they are taking 4-methylamphetamine. The reports that are available need to be interpreted with caution, as there was no analytical confirmation of the substances used.

Drugs Forum:
There is one user report describing use of 10–50 mg of a product that may have contained 4-methylamphetamine or 4-methylmethamphetamine (Drugs Forum, 2008). The individual reported 'headache, "din" [sic; possibly "pounding"] heart, nausea, nervousness and stimulation resembling ephedra'.

Bluelight:
This forum contains reports by users in France (Bluelight, 2008). It is noted that the majority of effects experienced by users are negative, with positive effects rarely reported. Variable effects include anxiety, immediately followed by a feeling of empathy and euphoria, with post-use effects such as insomnia, cognitive disorder and mood disorder. 'Ephedra-type' stimulant effects that are described by some users as 'terrible' with both physical and psychological effects: heavy sweating, nausea, abdominal pains, high blood pressure, flutter, headache, paranoia, hallucinations, anxiety and depression. No information is provided about other co-used substances, including medicines, that could explain these effects.

D1.2.2. Clinical acute 4-methylamphetamine toxicity

A total of 20 non-fatal cases of acute 4-methylamphetamine toxicity or detection of 4-methylamphetamine in drug-related offences have been reported from five Member States (Belgium, France, Hungary, Sweden and the United Kingdom). A further non-fatal intoxication that predates the Council Decision 2005/387/JHA was found in the literature (Bal et al., 1989) and is included here.

Non-fatal cases reported by Belgium:

- There is a report of a non-fatal intoxication in August 2011 related to consumption of a powder sold as 'speed'. No clinical details are available. Toxicological analysis revealed a blood concentration of 4-methylamphetamine 0.120 mg/L, no amphetamine detected, sildenafil positive.
- One non-fatal intoxication in August 2011. No clinical details were provided and no reported analysis of biological samples. Analysis of a powder collected as part of the investigation was found to contain 4-methylamphetamine (64 %), amphetamine (16 %) and caffeine (15 %).
- Report of a non-fatal intoxication in September 2011 with detection in urine of amphetamine and 4-methylamphetamine. No clinical details were provided in this report.
- Between July and August 2012, two intoxications occurred where trace amounts of 4-methylamphetamine were found. No clinical significance could be attached to the findings.

Non-fatal cases reported by France:

- June 2010, report of a 40-year-old male with depression with intravenous injection of 1.5 g of white paste over a 12-hour period that was believed to be amphetamine. 24 hours later he was admitted to hospital with nausea, sweating, paranoia and hallucinations, and symptoms of depression once the effects of the substance had subsided. Analysis of the paste showed amphetamine (10 %), 4-methylamphetamine (concentration not stated). The patient was also taking alcohol, cannabis, olanzapine, carbamazepine and methadone. No biological sample analysis was reported.

Non-fatal cases reported by Hungary:

- There are reports from 2012 of urine positive for 4-methylamphetamine and amphetamine in samples provided to the police from two individuals who were tested due to drug related offences. 4-Methylamphetamine concentrations, the circumstances of the testing or clinical features present were not reported.

Non-fatal cases reported by Sweden:

- Between April 2011 and March 2012 the National Board of Forensic Medicine analysed six urine samples that tested positive for 4-methylamphetamine; in all cases amphetamine was also detected. 4-Methylamphetamine concentrations, the circumstances of the testing or clinical features present were not reported.
- May 2012: four positive urine samples for 4-methyl-amphetamine reported from two different hospitals (Mälarsjukhuset and Västmanlandssjukhus hospital emergency wards) as part of the joint STRIDA project ([20]). 4-Methylamphetamine concentrations, the circumstances of the testing or clinical features present were not reported.

Non-fatal cases reported by the United Kingdom:

- April 2012: 20-year-old male (present with a 16-year-old female who died, see below) who was suspected to have used 4-methylamphetamine. Trace amount of amphetamine in the antemortem blood and medicines (administered at hospital) were detected. 4-Methylamphetamine detected in blood: 0.13 mg/L obtained some hours after consuming the drug. Also, mephedrone found in urine only. A further individual as part of this case (23-year-old male) also had a blood sample taken that detected trace amphetamine and 4-methylamphetamine (0.23 mg/L). Analysis of an off-white damp substance seized as part of the investigation detected 4-methylamphetamine and (<1 %) amphetamine.

Non-fatal cases reported in the literature:

- There is a single published case report of a 40-year-old male who reported snorting (nasal insufflation) 'amphetamine after consumption of five pints of lager and an unknown amount of sherry and barley wine' (Bal et al., 1989). Within a 'few minutes' started to feel unwell with a 'bad feeling in head, unable to focus eyes, dry mouth, palpitations' and his vision became bright and shimmery. On arrival in the emergency department, approximately one hour after use, he was noted to have sympathomimetic clinical features (tachycardia with heart rate of 150 beats per minute, hypertension with a blood pressure of 200/120 mmHg, dilated pupils and nystagmus). He was treated with the beta-blocker practolol; this reduced his heart rate to 115 but predictably worsened his hypertension to 240/160 mmHg. He was discharged from hospital within 48 hours, but appeared to have difficulty in sleeping and persistent feelings of extreme anxiety without obvious cause for several weeks after use. Analysis of powder by GC-MS detected 4-methylamphetamine and 4-methylmethamphetamine; there was no analysis of biological samples from the patient to confirm use and exclude concomitant use of other substances. It is not possible to determine whether the effects reported were due to 4-methylamphetamine, alcohol or 4-methylmethamphetamine.

([20]) See Bäckberg et al., (2011) for further details of the STRIDA project.

D1.2.3. 4-Methylamphetamine related deaths

The first death where 4-methylamphetamine was detected was from the United Kingdom in October 2010. There is limited clinical information in this case apart from that the deceased was sent home from work with 'flu-like symptoms' prior to death. Post-mortem toxicological screening was also positive for amphetamine and cannabis. To date, there have been a total of 21 deaths from four Member States: Belgium (6 deaths), Denmark (1), the Netherlands (6), and the United Kingdom (8) where 4-methylamphetamine alone or in combination with one or more other substance has been detected in post-mortem samples. Based on the information available it is not possible to determine the significance of the detection of 4-methylamphetamine in relation to the actual cause of death. There have been no reports of 4-methyl-amphetamine related deaths from other Member States, Croatia, Turkey and Norway. It should be noted that this may reflect that appropriate biological analysis has not been requested by the relevant authorities to determine whether 4-methylamphetamine is related to a death.

Reports from Member States concerning potential 4-methyl-amphetamine related fatalities are summarised below.

Belgium:

- A deceased individual (unspecified age and sex) was found in August 2011 with powder containing amphetamine, caffeine and 4-methylamphetamine. Blood concentration (not specified whether this was ante- or post-mortem) of 4-methylamphetamine 1.98 mg/L, amphetamine 1.70 mg/L, tetrahydrocannabinol (THC) 0.0024 mg/L and MDMA 0.23 mg/L. No further details were provided.
- A deceased individual (unspecified age and sex) used 'speed' in August 2011. Blood concentration (not specified whether this was ante- or post-mortem) of 4-methyl-amphetamine 1.2 mg/L, amphetamine 0.715 mg/L. No further details were provided.
- A deceased individual (unspecified age and sex) found in September 2011 with powder containing amphetamine, caffeine and 4-methylamphetamine. Blood concentration (not specified whether this was ante- or post-mortem) of 4-methylamphetamine 1.45 mg/L, amphetamine 0.75 mg/L and positive for olanzapine. No further details were provided.

- A 36-year-old male had a cardiorespiratory arrest in February 2012; no further clinical details were provided. Powder found on the individual contained amphetamine, 4-methylamphetamine and caffeine. Post-mortem tissue (not specified what tissue) was positive for amphetamine, 4-methylamphetamine and caffeine.
- A 34-year-old female in March 2012 was reported to have consumed ketamine, cocaine and amphetamines. She presented with 'extreme hyperthermia' and died after cardiac arrest; no further clinical details were provided. Powder found on the patient contained amphetamine and 4-methylamphetamine. Post-mortem tissue (not specified what tissue) was positive for amphetamine, 4-methylamphetamine, cocaine, benzoylecognine and levamisole. Pre-mortem femoral blood contained 4-methylamphetamine (0.62 mg/L), amphetamine (0.480 mg/L).
- A sixth death involving 4-methylamphetamine was reported in July 2012 concerning a 32-year-old male. 4-Methylamphetamine and amphetamine were detected in urine urine and 'high concentrations' of amphetamine were detected in blood. It is yet to be confirmed whether 4-methylamphetamine played a role in death and no further clinical details are available for this case.

In two of the four cases in which a powder sample that was recovered as part of the investigation was analysed and found to contain 4-methylamphetamine, amphetamine and caffeine, the active substances were quantified and 4-methyl-amphetamine was present in greater amounts than amphetamine (EMCDDA–Europol, 2012).

Denmark:

- A 27-year-old man was found dead in December 2010. Methylamphetamine was detected; it is not stated in which biological sample(s) or at what concentration. Nor was not possible to differentiate between 2-, 3- or 4-methyl-amphetamine. Additionally, amphetamine, morphine, methadone, THC and meta-chlorophenylpiperazine (*m*CPP) were detected; the concentrations of these were not stated, however these were reported to be 'found in doses which are seen in people abusing these substances'. Ephedrine was also found 'in an amount normally seen in people treated with this substance'. The forensic conclusion from the autopsy 'suggests that methylamphetamine was the cause of death as the estimated concentration is on a level that would be lethal if the substance in question was amphetamine'.

The Netherlands:

- Five deaths are reported in which post-mortem blood 4-methylamphetamine concentrations are available (four in 2011 and one in 2012). In a further death, no concentrations were reported. No clinical details or circumstances of these deaths are available.
  - 2011 Case 1: 4-methylamphetamine 1.4 mg/L, amphetamine 0.3 mg/L.
  - 2011 Case 2: 4-methylamphetamine 0.98 mg/L, amphetamine 1.7 mg/L.
  - 2011 Case 3: 4-methylamphetamine 2.3 mg/L, amphetamine 0.35 mg/L.
  - 2011 Case 4: 4-methylamphetamine 2.2 mg/L, amphetamine 0.04 mg/L, MDMA <0.01 mg/L.
  - 2012 Case 1: 4-methylamphetamine 0.5 mg/L, amphetamine 0.6 mg/L.
  - 2012 Case 2: 4-methylamphetamine and amphetamine detected (concentrations not reported for either).

The United Kingdom:

Eight deaths with analytical confirmation:

- October 2010: A 33-year-old male was sent home from work with flu-like symptoms. No further details are available. Post-mortem blood 4-methylamphetamine concentration 3.49 mg/L, amphetamine 16.5 mg/L and cannabis detected. No other drugs or alcohol detected. White powder submitted for analysis, found to contain 4-methylamphetamine and amphetamine.
- May 2011: A 22-year-old male had taken 'ecstasy' the night before and insufflated cocaine and 'M-CAT'. The patient was reported to be agitated, hot and shaking. Post-mortem blood 4-methylamphetamine concentration 3.77 mg/L, unidentified cathinones and ethanol 270 mg/L. No other drugs detected.
- January 2012: A 23-year-old female was found dead. There were indications that she had used ketamine and amphetamine but neither was detected at post-mortem. Post-mortem blood 4-methylamphetamine concentration 5.8 mg/L and ethanol 190 mg/L.
- April 2012: A 16-year-old female died in hospital following consumption of a yellow paste in a rizzla and swallowed (bombing). Ante- and post-mortem samples taken. Trace amount of amphetamine detected in the post-mortem blood, insufficient volume for ante-mortem measurement. 4-Methylamphetamine detected in blood (1.6 mg/L ante-mortem; 2.6 mg/L post-mortem). Possible explanations for the differences between ante- and post-mortem levels of the drug include: redistribution post-mortem and/or could still be ingesting the drugs due to ‹bolus›-type delivery from bombing. Analysis of an off-white damp substance seized as part of the investigation detected 4-methylamphetamine and amphetamine (<1 %). This case also involved two non-fatal intoxications, the details of which are presented above.

- May 2012: A 40-year-old male was found dead on the settee at home, having previously been noticed to have laboured breathing. He had been complaining of breathing trouble during the preceding few weeks. He had had a kidney transplant (not known when). Had begun to use recreational drugs (cannabis). Cannabinoids detected in blood. Amphetamine (1.1 mg/L) and 4-methylamphetamine (0.07 mg/L, low) were measured in femoral blood. Also detected were medicines: paroxetine, diazepam, metoclopramide, pseudo/ephedrine and quetiapine. Cause of death unclear.
- June 2012: A 29-year-old male was found dead on the ground near to a pumping station. Had sent a text to his partner inferring suicidal intent. 4-Methylamphetamine was found in urine only and not blood. Amphetamine (observed low/recreational level) was found in blood and urine. Caffeine detected in blood and urine at toxic (overdose) levels = 184 mg/L. No other drugs detected, alcohol urine only (340 mg/L).
- July 2012: A 43-year-old male was found in his work van in pain. Cardio-pulmonary resuscitation was started by a nurse who was a bystander. He was taken to hospital but was pronounced dead at the emergency department. He may have been an amphetamine user. Amphetamine detected in urine and blood (trace amount). 4-Methylamphetamine detected in urine only not blood. Cannabinoids detected in urine. No other drugs detected.
- July 2012: A 38-year-old male was found collapsed at his home address. Had a medical history of migraine, low mood and depression. 4-Methylamphetamine detected in blood (1.5 mg/L) and urine. Amphetamine detected in blood (trace amount) and urine. Paracetamol detected in blood and urine. No other drugs detected.

D2. Chronic health effects

D2.1. Animal data

In 30-day sub-acute and three-month chronic toxicity studies with 4-methylamphetamine administered orally to rats and dogs at up to 30 mg/kg daily doses, no evidence of changes were observed by histological examination of various tissues, including heart, kidney, liver, brain, and spleen (Fellows et al., 1950).

D2.2. Human data

There are no published studies investigating the chronic health effects of 4-methylamphetamine in humans to date. However, there is the potential for long-term physical harm as a direct result of acute 4-methylamphetamine toxicity (e.g. prolonged seizures resulting in cerebral hypoxia).

D3. Factors affecting public health risks

D3.1. Availability and quality of the new psychoactive substance on the market (purity, adulterants, etc.)

As summarised in Section C, 4-methylamphetamine is most commonly found in mixtures together with amphetamine and caffeine. 4-Methylamphetamine has been the only active substance in seized samples in only a few instances. This has been the case in some of the samples seized in Belgium, Denmark, France, Germany, Ireland, the Netherlands, Sweden and Croatia. In most cases, seized samples have not been quantitatively analysed and so the amount of 4-methylamphetamine detected has not been reported. As a result it is not possible to state the relative proportion of active ingredients in the seized products. In cases where the amount of 4-methylamphetamine has been determined, this has varied from trace or minor components to a small number of reports in which 4-methylamphetamine is reported as a larger or main component of the mixture. Additionally, apart from synthetic by-products, other substances that have been reported in 4-methylamphetamine seizures and collected samples include: lactose, paracetamol, ephedrine, cannabinol, tetrahydrocannabinol (THC), ketamine and 4-methylethcathinone (4-MEC).

Information on price is available from Austria, Belgium and the Netherlands (EMCDDA–Europol, 2012). In all of these cases the 4-methylamphetamine was sold as 'speed' (amphetamine). In Austria, four collected samples that contained 4-methylamphetamine (amphetamine was the main active substance present) cost between EUR 15 and EUR 30/gram. Belgium and the Netherlands reported that the prices were the same as for 'speed' (amphetamine) (EUR 10/gram).

A search of the anonymous online marketplace Silk Road ([21]) (June 2012), which specialises in the sale of products that would be unlawful in many jurisdictions without authority (particularly the sale of controlled drugs), did not find any 4-methylamphetamine being sold by sellers purporting to be from the United Kingdom (EMCDDA–Europol, 2012). None of the countries that reported seizures found to contain 4-methylamphetamine reported that these were linked to Internet sales (EMCDDA–Europol, 2012).

Germany, Italy and Sweden have reported that 4-methylamphetamine is being sold as a 'research chemical' on the Internet and France reported that 4-methylamphetamine availability on the Internet is low (EMCDDA–Europol, 2012). Italy also noted that 4-methylamphetamine was being offered for sale in classified adverts on the Internet in October 2011.

([21]) See Barratt (2012) and Christin (2012) for further information on 'Silk Road'.

Slovakia undertook a structured Internet search on 5 and 21 June 2012 in Slovak on two search engines (google.sk and zoznam.sk) (EMCDDA–Europol, 2012). Search terms (in Slovak) were: kupit '4-methylamphetamine' OR predate '4-methylamphetamine' OR obchod '4-methylamphetamine' OR trafficking with '4-methylamphetamine' ... '4-MA' or 'p-MA'. No websites selling or advertising 4-methylamphetamine were identified in this study.

The United Kingdom has reported that the FRANK drug information website (talktofrank.com) noted that 4-methylamphetamine has also been sold using the names 'ket phet' or 'phet ket'; however, an Internet search of these terms has yielded no drug-specific information (EMCDDA–Europol, 2012).

A structured search based on the EMCDDA snapshot methodology (EMCDDA, 2011) of the Internet sites balticnordic.com, tradekey.com and google.com using English search terms ('4-methylamphetamine', '4-ma', 'p-tap', 'pal-313', 'buy 4-methylamphetamine', 'buy 4-ma', 'buy p-tap', 'buy pal-313') was conducted by the EMCDDA on 18 July 2012. No sites were identified that sold 4-methylamphetamine aimed at users (i.e. as a 'legal high' or 'research chemical'). Websites were identified that sold 4-methylamphetamine as an analytical reference standard or for scientific research purposes. Some websites/web portals listed chemical suppliers that could purportedly offer 4-methylamphetamine for sale. No countries reported seizures or collected samples linked to sale of the drug on the Internet. Norway reported a single seizure by customs where 4-methylamphetamine was detected in a 'weight loss' product and they noted that this product is offered for sale on the Internet.

Where available, information from the fatal and non-fatal intoxication cases where 4-methylamphetamine has been detected suggests that the individual had attempted to source amphetamine ('speed') rather than specifically 4-methylamphetamine itself. Austria, Belgium, and the Netherlands have reported that 4-methylamphetamine has been sold at street level as 'speed' (amphetamine) and that there does not appear to be a specific demand for 4-methylamphetamine (EMCDDA–Europol, 2012).

Overall, based on this information, it is likely that most individuals are exposed to 4-methylamphetamine inadvertently after consuming an illicit amphetamine product that contains 4-methylamphetamine or a mixture of 4-methylamphetamine and other active substances (most commonly amphetamine and/or caffeine).

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

There is very limited information on commonly used Internet drug user discussion forums regarding the effects and potential health/adverse effects related to the use of 4-methylamphetamine. As previously noted, it appears that exposure to 4-methylamphetamine is generally inadvertent, occurring when individuals are attempting to source amphetamine ('speed'). Therefore, it is likely that the information, degree of knowledge and perceptions amongst users concerning 4-methylamphetamine and its effects are likely to be negligible.

D3.3. Characteristics and behaviour of users (including risk factors, vulnerability, etc.)

Since the majority of exposure/use of 4-methylamphetamine is likely to relate to where an individual attempts to source 'amphetamine' ('speed') and there are no surveys of 4-methylamphetamine users, there is no specific information as to the characteristics and behaviour of users of 4-methylamphetamine. However, it is likely that, given exposure is related to the attempted sourcing of 'amphetamine' ('speed'), the characteristics and behaviours of users should be considered to be comparable to those who use amphetamine.

D3.4. Nature and extent of health consequence (e.g. acute emergencies, road traffic accidents)

The very limited information on the acute health effects of 4-methylamphetamine were discussed in Section D1.2.

There is insufficient information in the reported fatalities where 4-methylamphetamine has been detected to discuss in detail the circumstances of these deaths. However, from the information available, it does not appear that any of these were related to road traffic accidents. One study notes the detection of 4-methylamphetamine in five serum samples of drivers in Germany (Westphal et al., 2011; Peters et al., 2011). However, further information on these cases is not available to allow additional comment.

D3.5. Long-term consequences of use

As discussed in Sections D2.1. and D2.2., there are no animal or human data on the chronic health effects of 4-methylamphetamine use. In particular, there have been no long-term follow-up studies to determine whether

4-methylamphetamine users are at greater risk of health deterioration later in life, or of developing chronic or life-threatening medical conditions.

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

As previously noted, it appears that the sourcing and use of 4-methylamphetamine generally related to individuals attempting to source amphetamine ('speed'). It is likely that 4-methylamphetamine is used in the same environments as amphetamine. This would be typically (but not restricted to) home environments, bars/pubs, discotheques/nightclubs and outdoor music festivals.

Section E. Social risks

E1. Individual social risks

There is no information available to determine the impact of 4-methylamphetamine in this area.

E2. Possible effects on direct social environment

There is no information available to determine the impact of 4-methylamphetamine in this area.

E3. Possible effects on society as a whole

There are five reports of 'minor crime' (concerning males aged 23, 39 and 40 and females aged 26 and 46) and one case of 'severe crime' (22-year-old male) from Sweden between April 2011 and March 2012. In addition to 4-methylamphetamine, other drugs were also reported (amphetamine in all cases, 'thc-acid' in two cases and benzodiazepine, buprenorphine and alcohol in one case). Information was not available to allow further comment. One study notes the detection of 4-methylamphetamine in five serum samples of drivers in Germany (Westphal et al., 2011; Peters et al., 2011). However, further information on these cases are not available to allow further comment.

E4. Economic costs

Given the lack of information available on acute health emergencies and healthcare utilisation related to the use of 4-methylamphetamine, it is not possible at this time to estimate whether 4-methylamphetamine is associated with greater healthcare costs than other stimulant drugs.

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

There is no information to be able to determine the impact of 4-methylamphetamine in this area.

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

At this time, there does not appear to be any specific demand for 4-methylamphetamine within the general population nor within sub-populations who are usually associated with higher use of recreational drugs and new psychoactive substances.

Section F. Involvement of organised crime

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

The available information suggests that 4-methylamphetamine is produced and trafficked by the same organised crime groups that are involved with the production and trafficking of amphetamine. However, there is no specific information that criminal groups are systematically involved in the production, trafficking and/or distribution of 4-methylamphetamine for financial gain (EMCDDA–Europol, 2012).

The only Member State to have reported the detection of illicit production of 4-methylamphetamine is the Netherlands. In 2010, 4-methylamphetamine was detected in three illicit amphetamine production laboratories. In August 2011, traces of 4-methylamphetamine were found at an amphetamine crystallisation site. It is not clear in these cases whether those involved in the production were aware that they were producing 4-methylamphetamine. However, information from Dutch police notes that some producers believed that they were attempting to produce amphetamine using the precursor BMK, but they were actually using 4-methyl-BMK, and, as a result, were inadvertently producing 4-methylamphetamine. No other countries reported illicit production of 4-methylamphetamine.

There have been five reports where 4-methylamphetamine that originated in the Netherlands was detected in seizures crossing

international borders to Germany, France and the United Kingdom. These seizures can be summarised as follows:

2011:
- 9 kg a yellow liquid containing 4-methylamphetamine and amphetamine seized in France whilst in transit from the Netherlands to the United Kingdom.
- 81.7 kg of a white paste containing 4-methylamphetamine, caffeine (19 %) and amphetamine seized in France whilst in transit from the Netherlands to Spain.
- 10 kg of a white powder found in a rental car entering Germany from the Netherlands. The powder was found to contain amphetamine, 4-methylamphetamine, caffeine and traces of 4-methyl-BMK. Intelligence in this case suggested that the arrested person had smuggled a few shipments of amphetamine to Germany and Spain in the preceding months.

2012:
- 2.22 kg of a powder containing amphetamine and 4-methoxyamphetamine was seized during a police check on an individual travelling from the Netherlands to Germany.
- 147 kg of paste containing 4-methylamphetamine, caffeine and amphetamine was seized in Lille, France whilst in transit to the United Kingdom. This is the largest seizure of 4-methylamphetamine reported to the EMCDDA and Europol.

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

The majority of seizures and detections have been of 4-methylamphetamine with amphetamine, often also with caffeine (as discussed above). There is nothing to suggest that distribution networks other than those established for amphetamine are being used. Based on the information available to ECMDDA and Europol, it does not appear that the production, trafficking and distribution of 4-methyl-amphetamine impacts on other existing psychoactive substances or new psychoactive substances, except amphetamine.

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

As discussed in above, the available information suggests that 4-methylamphetamine is produced and trafficked by the same organised crime groups that are involved with the production and trafficking of amphetamine (EMCDDA–Europol, 2012).

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

No information has been received by Europol on incidents of violence from criminal groups in connection specifically with 4-methylamphetamine.

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

No information has been received by Europol on incidents of money-laundering specifically in connection with 4-methylamphetamine.

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

There is no information available to determine the impact of 4-methylamphetamine in this area.

F7. Use of violence between or within criminal groups

There is no information available to determine the impact of 4-methylamphetamine in this area.

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

There is no information available to determine the impact of 4-methylamphetamine in this area.

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ANNEX 2

Computational analysis on the pharmacology of 4-methylamphetamine

Fazlin Mohd Fauzi and Dr Andreas Bender

Introduction

The effect of a drug results from the interaction between the drug and one or more protein targets, which then triggers a biochemical response and, eventually, the desired effect for the drug user. Hence, by knowing which protein targets a drug may bind to, we can predict and rationalise the effects that a drug may cause to a person. In this analysis of 4-methyl amphetamine, we utilised our *in silico* target prediction algorithm which is able to anticipate drug targets given a chemical structure. The predicted targets can then be used to elucidate possible effects or mechanism-of-action, in addition to possible side effects of 4-methylamphetamine.

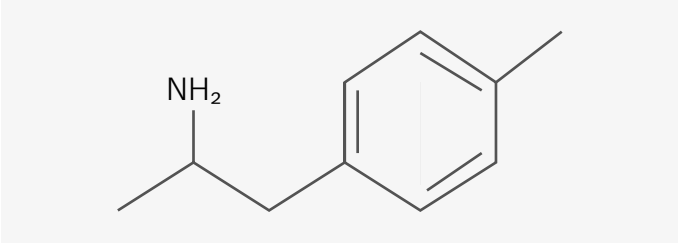
How psychoactive drugs affect the brain

When applied in a recreational setting, drug users generally seeks the 'high' effect which produces the feeling of pleasure when consuming psychoactive drugs (1). The reward circuit, which consists of brain structures that regulate and control this pleasurable effect, is located in the limbic part of the brain (1) and it is stimulated by neurotransmitters, in particular dopamine and serotonin, but also others such as noradrenaline (2). Psychoactive substances such as MDMA (methylenedioxymethylamphetamine, commonly known as 'ecstasy') and cocaine increase the level of the above neurotransmitters, hence over-stimulating the reward circuit in a variety of ways (2). MDMA does this by blocking the clearance or re-uptake of serotonin from the synapses of the nerve cells while cocaine blocks the re-uptake of dopamine, in addition to serotonin and noradrenaline (2).

Analysis of 4-methylamphetamine

FIGURE A1

The chemical structure of 4-methylamphetamine



We subjected the compound to be assessed, 4-methyl-amphetamine, to a target prediction algorithm to anticipate its effects in man. For this purpose, the top 20 protein targets anticipated for 4-methylamphetamine were analysed as follows:

1. Serotonin transporter
2. Monoamine oxidase A
3. Indoleamine 2,3-dioxygenase
4. Tyrosine-protein kinase CSK
5. Monoamine oxidase B
6. Carbonic anhydrase II
7. Carbonic anhydrase I
8. Carbonic anhydrase XII
9. Carbonic anhydrase III
10. Carbonic anhydrase VA
11. Estrogen receptor beta
12. Estrogen receptor alpha
13. Nitric oxide synthase, inducible
14. Nitric-oxide synthase, endothelial
15. Nitric-oxide synthase, brain
16. Aminopeptidase N
17. Carbonic anhydrase VB
18. Carbonic anhydrase IX
19. Carbonic anhydrase IV
20. Arachidonate 15-lipoxygenase

Possible mechanism-of-action of 4-methylamphetamine

From the list of the top 20 targets predicted for 4-methyl-amphetamine, it is hypothesised that 4-methylamphetamine increases the level of neurotransmitters in the reward circuit *via* the following mechanisms:

- The inhibition of serotonin transporter (SERT), which is responsible for the re-uptake of serotonin. Blocking SERT increases the level of serotonin in the nerve terminals, consequently over-stimulating the reward circuit (3). MDMA and paramethoxyamphetamine (PMA), which, like 4-methylamphetamine, are analogues of amphetamine, also block serotonin reuptake (2, 4, 5). PMA is abbreviated by some authors as 4-MA, therefore that abbreviation is not used in this report for 4-methylamphetamine due to the potential for confusion of the two.
- The inhibition of both monoamine oxidase (MAO) A and B. These enzymes are responsible for the conversion of monoamine-based neurotransmitters into their inactive forms, which are not able to stimulate the reward circuit any further (6). MAO A is responsible for the metabolism of serotonin, dopamine and noradrenaline while MAO B solely metabolises dopamine, and, given the anticipated activity on both targets, effects on all neurotransmitters listed are to be expected (6). The inhibition of MAO and the consequential effects have also been observed when amphetamine is consumed (5, 7). PMA solely blocks MAO A, with no activity noted on MAO B and is 20 times more potent at inhibiting MAO A than amphetamine (K_i = 0.22µM *in vitro*) (8).

It is worth noting here that dopamine transporter (DAT), which has been found to interact with amphetamine (9), was not predicted here. The interaction between DAT and amphetamine blocks the clearance or re-uptake of dopamine, causing the increase of dopamine level in the brain (10). As amphetamine and 4-methylamphetamine are structurally similar, there is a possibility that 4-methylamphetamine may also interact with DAT. This implies that while the *in silico* target prediction was able to generate targets relevant to 4-methylamphetamine, i.e. SERT and MAO, our model may not fully cover the biological space relevant to the chemical structure of 4-methylamphetamine. This limitation will be discussed further at the end of this section.

Possible toxicities of 4-methylamphetamine

Serotonin syndrome

Some possible toxicities of 4-methylamphetamine due to the elevated level of serotonin in the brain are listed in Table A1. These effects resembles the serotonin syndrome often seen in PMA (5) and amphetamine users (11) and may be seen within an hour of administration.

TABLE A1

The acute toxicities anticipated for 4-methylamphetamine based on the targets predicted, such as euphoria, hyperthermia and anorexia. These effects resemble the serotonin syndrome often seen in amphetamine, methamphetamine and PMA users (5,11).

Acute toxicity	Notes
Euphoria	Increased dopamine and serotonin levels stimulate the reward circuit in the limbic system, hence producing the feeling of euphoria (2).
Hyperthermia	Serotonin and dopamine stimulates the thermal regulatory circuit in the hypothalamus causing an increase in body temperature (12, 13). PMA have been found to dramatically increase body temperature, thought to be due to the dramatic increase of serotonin through the concurrent inhibition of serotonin re-uptake and MAO A serotonin conversion (5, 8).
Anorexia	A high level of serotonin in the hypothalamus has been found to reduce appetite (3, 6). In addition, it was found that anorexic patients show high level of serotonin in the brain (14).
Hallucinogenic	Hallucinations are expected due to the stimulation of the frontal cortex and visual cortex by both serotonin and dopamine (4).
Decreased fatigue, increase arousal, insomnia	These toxic effects are caused by the high level of noradrenaline, adrenaline and dopamine (collectively known as catecholamine) (3, 6).
Locomotor stimulation/hyperactivity	These effects are a result of high level of dopamine (15), which is rarely seen in PMA users as this compound has only a weak effect on dopamine levels (16).

From Table A1, it can be seen that by knowing the targets modulated by a drug, in this case 4-methylamphetamine, we can then establish possible side effects in addition to mechanism-of-action. Using anorexia as a symptom to illustrate this, 4-methylamphetamine is likely to increase the level of serotonin available in the synapses. High levels of serotonin in the hypothalamus have been found to reduce appetite (3, 6) and it was found that anorexic patients showed high level of serotonin in the brain (14). Additionally, as amphetamine was once marketed as a diet pill as it suppresses the appetite (17), we rationalise that anorexia may be a potential toxicity for 4-methylamphetamine as well. Interestingly, fenfluramine, another amphetamine analogue, was also once marketed as a diet pill and a safer alternative to amphetamine, which was taken off the market due to abuse potential (17). In addition, fenfluramine was found to cause devastating long-term side effects to the heart, lungs and nerves (17–19).

'Amphetamine psychosis'

When amphetamine is repeatedly taken over several days, symptoms resembling an acute schizophrenic attack, i.e. paranoia, hallucinations and aggressive behaviour where drug users are detached from reality, can occur (3), an effect known as 'amphetamine psychosis' (3). Psychosis is also seen in long-term methamphetamine users (4). From the targets predicted for 4-methylamphetamine, in particular indoleamine-2,3-deoxygenase (IDO), amphetamine psychosis may be a possible toxicity of 4-methylamphetamine given that IDO is a target for the treatment of schizophrenia (20). It has been found that in schizophrenic patients the level of IDO is reduced while tryptophan-2,3-deoxygenase (TDO) is elevated, and both enzymes are responsible for the metabolism of tryptophan. When IDO is blocked, tryptophan is predominantly metabolised by TDO, subsequently producing the metabolite kynurenine acid (KYNA) (20, 21). KYNA is an endogenous N-methyl-D-aspartate (NMDA) receptor antagonist which upon binding to the NMDA receptor causes an increase in dopaminergic activity and decrease in glutaminergic activity, leading to psychosis (20). This effect can also be seen when ketamine, an exogenous NMDA receptor antagonist, is taken (20). In addition, KYNA also blocks the α-7-nicotinic acethylcholine receptors, which causes cognitive impairment (20).

Cardiac-related complications

As postulated earlier in 'Possible mechanism-of-action of 4-methylamphetamine', 4-methylamphetamine increases the level of neurotransmitters, i.e. serotonin, dopamine and noradrenaline (2). An increase in noradrenaline has been found to be connected to cardiac related complications (22). Noradrenaline increases heart contraction and heart rate, constrict blood vessels and causes platelet aggregation, leading to blood clot (22). These effects can lead to complications such as arrhythmia (irregular heartbeat), hypertension (high blood pressure) as well as myocardial infarction (heart attack) where the blood supply to the heart is blocked, causing heart cells to die (3). Acute myocardial infarction has been reported in patients injecting themselves with amphetamine, which was seen an hour after injection (22, 23). In addition, the hypertensive effect of noradrenaline can also be extended to the blood vessels in the brain, causing cerebral hypertension (4). This can lead to complications such as cerebrovascular accident (stroke), which has been reported in conjunction with the use of MDMA (24) and amphetamine (25).

In addition to the increase in noradrenaline, the inhibition of endothelial nitric oxide synthase (eNOS) by 4-methyl-amphetamine was found to also cause both hypertension and myocardial infarction (6). eNOS produces the compound nitric oxide (NO) in the blood vessel (6). NO causes the dilation of blood vessel and is also an anti-atherogenic where it prevents the build-up of plaque in the blood vessel, hence reducing the likelihood of myocardial infarction (26). In a study by Archer et al. (27), it was found that deficiency of NO was seen in patients diagnosed with pulmonary hypertension who had also stopped taking fenfluramine and dexfenfluramine for several years. The reason for this was not established in the study but from the results of the target prediction we reasoned that this may be due to the interaction between the amphetamine analogues and eNOS.

Neurotoxicity

Long-term use of MDMA causes enhanced release of dopamine in the brain, which can be damaging to neurons and in particular the serotonergic neuron in the striatum (28, 29). In addition, MDMA also causes 2-hydroxybenzoic acid (salicylic acid) to be hydrolysed to 2,3-dihydroxybenzoic acid, a free radical that can damage the serotonergic neurons (30). The damage to the serotonergic nerve damage has been found to have an effect on verbal memory. In a study done on MDMA users who had ceased from using the drug for a mean of three years, little improvement was seen on the verbal memory test (31). In addition, in a study done by Ernst et al. (32), methamphetamine (N-methylamphetamine), which is neurotoxic to both dopaminergic and serotonergic neurons, showed that this is a long-term effect even in N-methamphetamine users who had since abstained.

Other possible effects of 4-methylamphetamine

Although the literature support for the possibility of amphetamine and its analogue to be carcinogenic is still

lacking, based on the prediction of aminopeptidase N, carbonic anhydrase, protein tyrosine kinase Csk and arachidonate 15-lipoxygenase, 4-methylamphetamine may also cause cancer (though given the acute effects, this might only sometimes be relevant in practical settings). Aminopeptidase N have been found to be over expressed in non-small lung, colon and prostate cancer cells (33). Carbonic anhydrase catalyzes the conversion of water and carbon dioxide into bicarbonate and the clinical significant of the subtypes of this enzyme is still unclear (34). However, carbonic anhydrase XII have been found to regulate the acidity of the microenvironment in cancer cells, which modulates tumour malignant phenotype (34). In addition, it was found that CA12 is over expressed in renal cancer cells (35) and breast cancer cells (34). Protein tyrosine kinase Csk has been suggested to be an antioncogene; it down regulates the expression of oncogenes that can lead to cancer transformation (36). In addition, arachidonate 15-lipoxygenase was found to suppress the progression of prostate cancer (37). Arachidonate 15-lipoxygenase has also been found to be highly expressed in the airways of asthmatic patients, suggesting possibly causing inflammation of the airways (38).

Tolerance and dependence potential of 4-methylamphetamine

After prolonged use, amphetamine and N-methamphetamine abusers develop tolerance and decrease susceptibility towards the effect of the drug (3, 5) due to the depletion of neurotransmitters i.e. serotonin and dopamine in the brain after prolonged use. Due to the tolerance developed, users tend to increase drug intake, hence becoming dependent to achieve the 'high' effect, which is often the case in amphetamine users (3). Given the similar bioactivity spectra expected for 4-methylamphetamine, compared to amphetamine, similar dependence potential is predicted.

Limitations of the study

The target prediction performed here covers a relatively large biological space comprising 894 protein targets. Each of these protein targets is represented by relevant chemical spaces, which are defined by particular chemical structures. Given the computational procedure performed here, we still need to establish the extent to which the chemical space in the target prediction is representative of the chemical structures specific to psychoactive drugs, in order to have a high confidence in the predictions generated. While a general validation of the target prediction algorithms used here has already been performed, this step will be the further explored in the near future.

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Council Decision

Council Decision 2013/129/EU of 7 March 2013 on subjecting 4-methylamphetamine to control measures

THE COUNCIL OF THE EUROPEAN UNION,

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

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

Having regard to the initiative of the European Commission,

Whereas:

(1) A Risk Assessment Report on 4-methylamphetamine was drawn up on the basis of Article 6 of Decision 2005/387/JHA by a special session of the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction, and was subsequently received by the Commission on 29 November 2012.

(2) 4-methylamphetamine is a synthetic ring-methylated derivative of amphetamine which has predominantly been seized in powder and paste form in samples containing amphetamine and caffeine, but which has also appeared in tablet and liquid form. It has emerged on the illicit amphetamine market where it is sold and used as the controlled drug, amphetamine. There has been one report of the substance being detected in a commercial product sold on the internet. The main chemical precursor for the synthesis of 4-methylamphetamine is 4-methylbenzyl methyl ketone (4-methyl-BMK), which appears to be commercially available on the internet and is not controlled under the 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

(3) The specific physical effects of 4-methylamphetamine have been rarely reported by users, since users are typically unaware that they have taken the substance. However, the few reports that are available suggest that it has stimulant-type effects. Limited data available relating to humans suggest that the adverse effects of 4-methylamphetamine include hyperthermia, hypertension, anorexia, nausea, perspiration, gastric distress, coughing, vomiting, headache, palpitations, insomnia, paranoia, anxiety and depression. Current data is not sufficient to determine the relative dependence-producing potential of the substance.

(4) According to the limited data sources available, the acute toxicity of 4-methylamphetamine is similar to that of other stimulants. Certain evidence suggests that a combination of 4-methylamphetamine with other substances, including amphetamine and caffeine, may result in a higher risk of overall enhanced toxicity.

(5) There have been a total of 21 fatalities registered in four Member States where 4-methylamphetamine alone, or in combination with one or more substances, especially amphetamine, has been detected in post-mortem samples. While it is not possible to determine with certainty from the information available the role of 4-methylamphetamine in those fatalities, in some cases the substance was the predominant drug detected, with

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

levels comparable to those found in certain cases of death caused by the consumption of amphetamine.

(6) 4-methylamphetamine has been detected in 15 Member States, while one Member State has reported the manufacture of the substance on its territory. Prevalence specific to 4-methylamphetamine is difficult to estimate. There is no information on specific demand for the substance from user groups and it is not commercially marketed through internet shops.

(7) The information available suggests that 4-methylamphetamine is produced and distributed by the same organised crime groups that are involved in the manufacture and trafficking of amphetamine.

(8) 4-methylamphetamine has no known, established or acknowledged medical value or use in the Union and there is no marketing authorisation for the substance in the Union. Apart from its use as an analytical reference standard and in scientific research, there is no indication that it may be used for any other legitimate purpose.

(9) 4-methylamphetamine is not currently under assessment and has not been under assessment by the United Nations system. Eight Member States control the substance under drug control legislation by virtue of their obligations under the 1971 United Nations Convention on Psychotropic Substances. Two other Member States apply the generic definition of phenethylamine in their national legislation to the product while one Member State controls it under its medicines legislation.

(10) The Risk Assessment Report reveals that there is limited scientific evidence available on the characteristics and risks of 4-methylamphetamine and points out that further studies are required on the overall health and social risks associated with the substance. However, the evidence available provides sufficient grounds for subjecting 4-methylamphetamine to control measures across the Union. As a result of the health risks it poses, as documented in its detection in several reported fatalities, especially when used in combination with other substances; its strong resemblance in terms of appearance and effects with amphetamine; the fact that users may unknowingly consume the substance and its limited medical value or use, 4-methylamphetamine should be subjected to control measures across the Union.

(11) Since 10 Member States already control 4-methylamphetamine, subjecting it to control measures across the Union may help avoid problems in cross-border law enforcement and judicial cooperation.

(12) Union-wide control measures may also help prevent 4-methylamphetamine developing as an alternative to amphetamine in the illicit drug markets,

HAS ADOPTED THIS DECISION:

Article 1

The new psychoactive substance, 4-methylamphetamine, is hereby subjected to control measures across the Union.

Article 2

By 17 March 2014, Member States shall take the necessary measures, in accordance with their national law, to subject 4-methylamphetamine to control measures and criminal

penalties, as provided for under their legislation complying with their obligations under the 1971 United Nations Convention on Psychotropic Substances.

Article 3

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

Done at Brussels, 7 March 2013.

For the Council
The President
A. SHATTER

Abbreviations	
4-MA	4-methylamphetamine
4-MEC	4-methylethcathinone
4-methyl-BMK	4-methylbenzyl methyl ketone
5-HT	5-hydroxytryptamine
5-HTP	5-hydroxytryptophan
APAAN	alpha-phenylacetoacetonitrile
API	active pharmaceutical ingredient
BMK	benzyl methyl ketone
CA12	carbonic anhydrase XII
CAS	Chemical Abstracts Service registry number
DAT	dopamine transporter
Decision	Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances
DIMS	Drugs Information and Monitoring System (Netherlands)
DOM	2,5-dimethoxy-4-methylamphetamine
DPIA	diphenylisopropylamine
EC_{50}	half maximal effective concentration
ED_{200}	the dose required to cause a 200 % increase in motor activity
EMA	European Medicines Agency
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
eNOS	endothelial nitric oxide synthase
ENU	Europol National Units
ESPAD	European school survey project on alcohol and other drugs
EUR	Euro
EWS	Early-warning system (EMCDDA–Europol)
GC	gas chromatography
GC-MS	gas chromatography–mass spectrometry
IDO	indoleamine-2,3-deoxygenase
IUPAC	International Union of Pure and Applied Chemistry

Abbreviations	
K_i	dissociation constant
KYNA	kynurenine acid
LC	liquid chromatography
LC-MS/MS	liquid chromatography tandem mass spectrometry
LD_{50}	median lethal dose
LSD	lysergic acid diethylamide
MAO	monoamine oxidase
mCPP	meta-chlorophenylpiperazine
MDMA	3,4-methylenedioxymethylamphetamine
Meth	N-methylamphetamine
mmHg	millimeter of mercury
MS	mass spectrometry
NFP	national focal point of the Reitox network
NMDA	N-methyl-D-aspartate
NMR	nuclear magnetic resonance spectroscopy
NO	nitric oxide
PAL-303	4-fluoroamphetamine
PAL-313	4-methylamphetamine
PAL-314	3-methylamphetamine
PAL-353	3-fluoroamphetamine
PMA	para-methoxyamphetamine
p-MA	para-methylamphetamine or 4-methylamphetamine
PNMT	phenethanolamine N-methyltransferase
SERT	serotonin transporter
TDO	tryptophan-2,3-deoxygenase
THC	tetrahydrocannabinol
UN	United Nations
USD	US dollars
WHO	World Health Organization

Participants of the risk assessment meeting, 16 November 2012

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- **David Friggieri,** Anti-Drugs Policy Unit, European Commission, Brussels
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EMCDDA

- **Paul Griffiths,** Scientific director
- **Roumen Sedefov,** Head of unit, Supply reduction and new trends unit

Invited external experts

- **Dr Peter Blanckaert,** Coordinator, Belgian Early Warning System on Drugs
- **Dr Jan Van Amsterdam,** National Institute for Public Health and the Environment (RIVM), Bilthoven

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- **Ana Gallegos,** Scientific analyst, Action on new drugs, Supply reduction and new trends unit
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TD-AK-13-001-EN-N

Recommended citation:

European Monitoring Centre for Drugs and Drug Addiction (2014), *Report on the risk assessment of 4-methylamphetamine in the framework of the Council Decision on new psychoactive substances*, Risk Assessments, Publications Office of the European Union, Luxembourg.

About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction is the hub of drug-related information in Europe. Its mission is to provide the European Union and its Member States with 'factual, objective, reliable and comparable information' on drugs and drug addiction and their consequences. Established in 1993, it opened its doors in Lisbon in 1995, and is one of the European Union's decentralised agencies. The Centre 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.

Related publications and websites

EMCDDA

- European Drug Report 2013
- Risk assessment of new psychoactive substances — operating guidelines, 2010

EMCDDA and Europol

- EMCDDA–Europol 2012 Annual Report on the implementation of Council Decision 2005/387/JHA (New drugs in Europe, 2012)
- EMCDDA–Europol Joint Report on a new psychoactive substance: 4-methylamphetamine, 2012

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

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Luxembourg: Publications Office of the European Union
doi:10.2810/86512 | ISBN 978-92-9168-601-8

This publication is only available in electronic format.

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ISBN 978-92-9168-601-8
9 789291 686018

Publications Office