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Its role is to gather, analyse and disseminate 'objective, reliable and comparable information' on drugs and drug addiction and, in doing so, provide its audiences with a sound and evidence-based picture of the drug phenomenon at European level.

Among the Centre's target groups are policy-makers who use this information to help formulate coherent national and Community drug strategies. Also served are professionals and researchers working in the drugs field and, more broadly, the European media and general public.

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Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

EMCDDA
RISK ASSESSMENTS

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European Monitoring Centre
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A great deal of additional information on the European Union is available on the Internet. It can be accessed through the Europa server (<http://europa.eu.int>).

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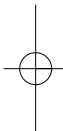


European Monitoring Centre
for Drugs and Drug Addiction

Rua da Cruz de Santa Apolónia 23-25, P-1149-045 Lisbon
Tel. (351) 218 11 30 00 • Fax (351) 218 13 17 11
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Foreword

It gives me particular pleasure to present the results of the risk assessment undertaken by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the substance para-methoxymethamphetamine (PMMA). The risk assessment was carried out under the terms of a joint action adopted on 16 June 1997 by the Council of the European Union (EU) ⁽¹⁾.

The meeting to assess the risks of PMMA was convened under the auspices of the Scientific Committee of the EMCDDA and was held on 29 October 2001 at the Centre's headquarters in Lisbon. It is the fifth such exercise undertaken to date by the EMCDDA ⁽²⁾.

The meeting resulted in a formal 'Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs', which was drawn up and adopted the same day by the meeting. The report was submitted the following day to the Belgian Presidency of the horizontal working party on drugs of the Council of the EU and to the European Commission for further action, as foreseen in the joint action.

As a result of the evidence and conclusions presented in the report, in December 2001, the European Commission presented an initiative to the Council to make PMMA subject to measures of control in all Member States.

On 28 February 2002, the Council adopted the decision ⁽³⁾ to submit PMMA to control measures and criminal penalties in the 15 EU countries. The Council decision stipulates that, within three months, Member States shall introduce the necessary measures in their national law, in compliance with their obligations under the 1971 United Nations (UN) Convention on Psychotropic Substances. Since 13 September 1999, one other new synthetic drug, 4-MTA, has similarly been subject to control measures by a Council decision in the framework of the joint action of 16 June 1997.

⁽¹⁾ Joint action concerning the 'information exchange, risk assessment and the control of new synthetic drugs' (OJ L 167, 25.6.1997). A joint action is a decision adopted unanimously by the EU Member States within the framework of the third pillar of the Treaty on European Union (cooperation in the field of justice and home affairs). Synthetic drugs are psychoactive substances produced in laboratories and not derived from natural products. They include 3,4-methylenedioxy-N-methylamphetamine (MDMA, 'ecstasy'), other amphetamines and lysergic acid diethylamide (LSD).

⁽²⁾ The four previous risk assessment exercises concerned the substances N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), 4-methylthioamphetamine (4-MTA), gamma-hydroxybutyric acid (GHB) and ketamine.

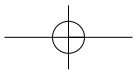
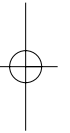
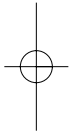
⁽³⁾ It came into effect on 7 March 2002.

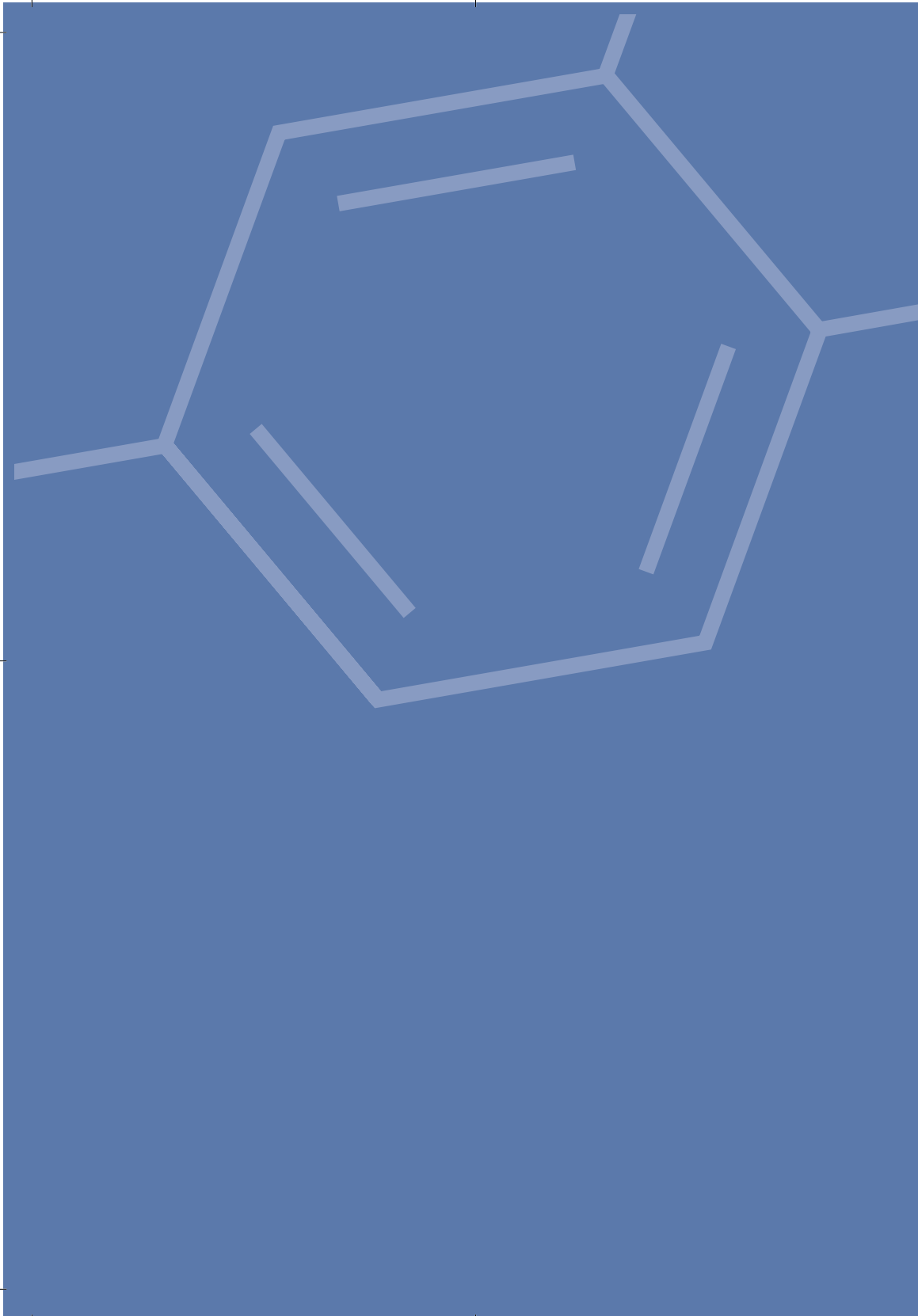
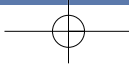
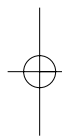
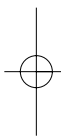
Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

Such a concrete result at a political level confirms the effectiveness of the rapid-response mechanism provided by the joint action on new synthetic drugs. It also provides strong encouragement for the development over the last four years of sound cooperation between the EMCDDA and its institutional partners involved in the risk assessment process, including the European Police Office (Europol), the European Agency for the Evaluation of Medicinal Products (EMA) and the European Commission. In particular, I would like to underline the excellent work done by the EMCDDA's early-warning system via the European network of national focal points and through Europol's national units, which collected information on the social and health aspects of the drug and implications for illegal drugs trafficking.

I would like to thank all those who participated in the risk assessment process for PMMA for the high quality of the work carried out. This makes a valuable scientific contribution, validated at European level, based on knowledge of MDMA analogues and, as such, gives proven support to political decision-making.

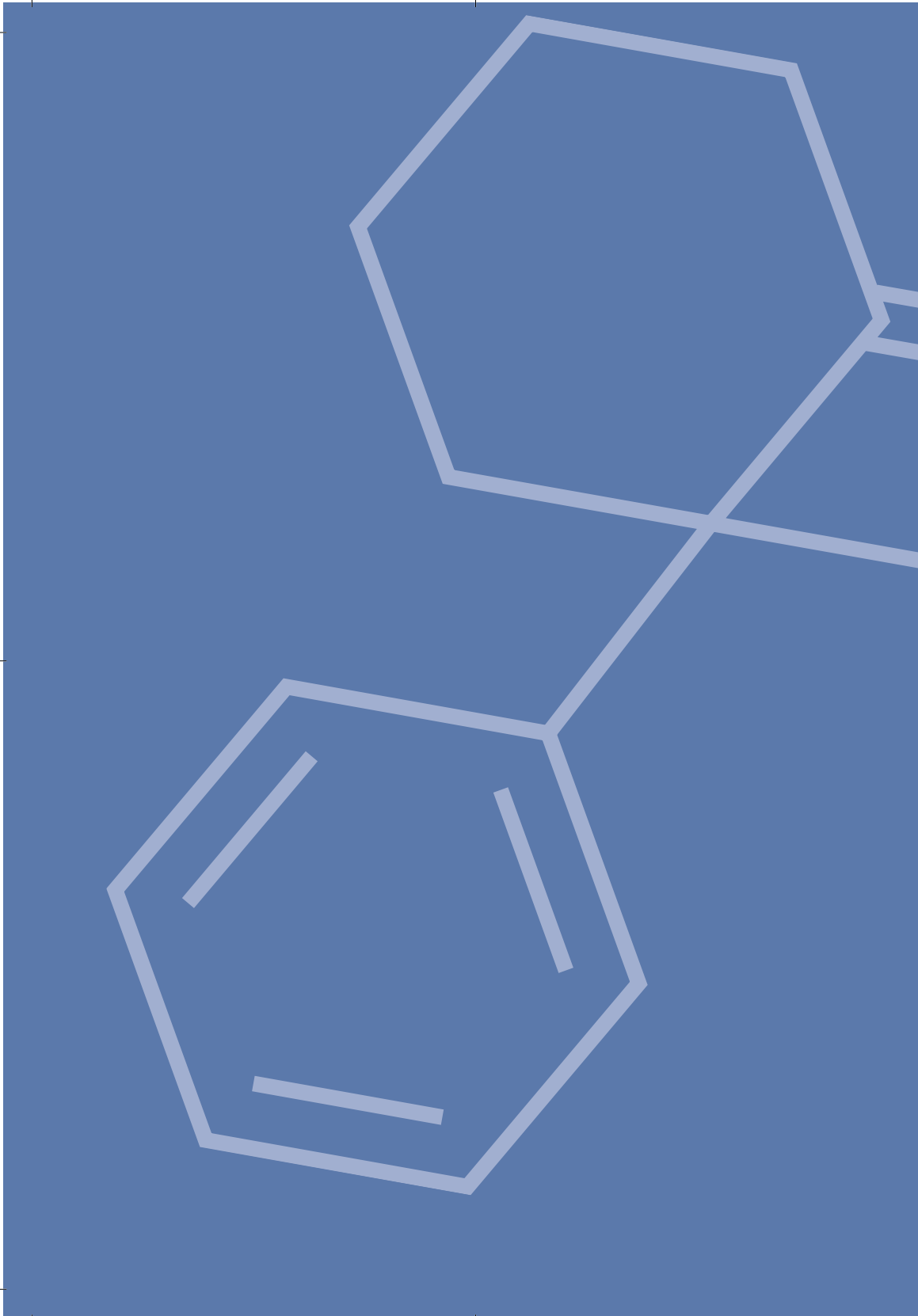
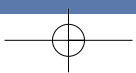
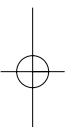
Georges Estievenart
Executive Director, EMCDDA





Abbreviations

BKA	Bundeskriminalamt
CAM	Coordination Centre for Assessment and Monitoring of New Drugs of Misuse
DEA	Drugs Enforcement Administration
Europol	European Police Office
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EMA	European Agency for the Evaluation of Medicinal Products
Reitox	European information network on drugs and drug addiction
3,4 DMA	3,4-dimethoxyamphetamine
4-MTA	4-methylthioamphetamine
5-HT	5-hydroxytryptamine, serotonin
5-HIAA	5-hydroxyindoleacetic acid
AUC	area under the plasma concentration–time curve
BP	blood pressure
DOM	4-methyl-2,5-dimethoxyamphetamine
EC	effect concentration
GC–MS	gas chromatography–mass spectrometry
GHB	gamma-hydroxybutyric acid
K_i	inhibitory constant
LD	lethal dose
LSD	lysergic acid diethylamide
MA	methoxyamphetamine
MAO	monoamineoxidase
MBDB	N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine
MDA	3,4-methylenedioxyamphetamine
MDEA	3,4-methylenedioxy-N-ethylamphetamine
MDMA	3,4-methylenedioxy-N-methylamphetamine, 'ecstasy'
PMA	para-methoxyamphetamine
PMMA	para-methoxymethamphetamine
p-OH-AMP	para-hydroxyamphetamine



Introduction

Since June 1997, the date on which the Council of the EU for joint action adopted recommendations concerning the information exchange, risk assessment and control of new synthetic drugs, PMMA is the fifth product to have undergone the risk assessment procedure. Previously, the extended Scientific Committee of the EMCDDA had performed risk assessments on MBDB, 4-MTA, ketamine and GHB.

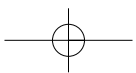
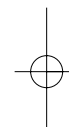
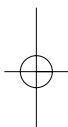
Unlike ketamine and GHB, but similar to MBDB and 4-MTA, PMMA is one of the numerous 'new synthetic drugs' with no legitimate therapeutic use that are described in Shulgin's *Pihkal* (Shulgin and Shulgin, 1991). PMMA is a structural hybrid of PMA (para-methoxyamphetamine) and methamphetamine and, although chemically analogous to MDMA, it has one oxygen atom removed. Thus it lacks the important methylenedioxy group present in MDMA. An overview of the scientific literature on the pharmacology and toxicology of PMMA in animals as well as on the human pharmacology, clinical experience and psychological risks of PMMA use was compiled by Professor Hans Rommelspacher from the Free University of Berlin in Germany. This overview was extended by a thorough review, conducted by Europol and the EMCDDA in association with the various Reitox national focal points, of the pharmacotoxicological, sociological and criminological information available on PMMA. The main difficulty encountered by experts was the relatively small amount of data existing in the literature for PMMA compared with that available for PMA. However, since both products occur in association in 'ecstasy'-like tablets and present similar pharmacological characteristics, experts agreed to extrapolate some of the data obtained for PMA to PMMA. A preparatory technical expert meeting with members of the subcommittee for risk assessment was first held on 8 October 2001. Then, members of the Scientific Committee of the EMCDDA plus experts nominated by the Member States and representatives of the European Commission, of Europol and of the EMEA met in Lisbon on 29 October 2001 to discuss the health and social risks of PMMA as well as the possible consequences of its prohibition. The risk assessment report on PMMA was adopted by this assembly that same day.

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

As Chair and Vice-Chair of the Scientific Committee, we would like to express our gratitude to our colleagues on the Scientific Committee as well as to the staff of the Centre and, in particular, to Alain Wallon, Lena Westberg and Deborah Olszewski, who worked hard before, during and after the meetings, to finalise the reports in order to ensure detailed and precise conclusions and a speedy transmission. We hope that all these efforts will be appreciated by those to whom this report is addressed.

Salme Ahlström and Jean-Pol Tassin

Chairperson and Vice-Chairperson, Scientific Committee of the EMCDDA





Chapter 1

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

A meeting of the Scientific Committee of the EMCDDA, extended with experts nominated by the Member States and representatives of the European Commission, Europol and the EMEA, was held on 29 October 2001. This meeting sought to assess the health and social risks of PMMA, especially in association with PMA, as well as to assess the possible consequences of prohibition. This meeting was subsequent to the formal notification of the Swedish Presidency of the Council of the EU requesting a risk assessment of PMMA under Article 4 of the joint action on new synthetic drugs of 16 June 1997.

The meeting considered the following documents:

- i. Technical Annexes A and B: the pharmacotoxicological report on PMMA; report to the EMCDDA
- ii. Technical Annex D: public health risks: epidemiological evidence; EMCDDA
- iii. Technical Annex C: sociological/criminological evidence; EMCDDA
- iv. Europol contribution to the risk assessment on PMMA

In conjunction with further information and comments provided by the expert participants, these documents formed the basis of the risk assessment which is reported below.

Chemical description

PMMA is para-methoxymethylamphetamine or N-methyl-1-4-(methoxyphenyl)-2-aminopropane. Other chemical names are 4-methoxy-N-methyl-amphetamine (4-MMA) and 2-methylamino-1-(p-methoxyphenyl)-propane. It is a structural hybrid of two phenylisopropylamine stimulants: PMA and methamphetamine. Precursors and reagents include 4-methoxyphenylacetone (4-methoxyphenyl-2-propanone), methylamine hydrochloride, sodium cyanoborohydride, ethyl chloroformate and formic acid.

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PMA is para-methoxyamphetamine or 4-methoxyamphetamine (4-MA). Another chemical name is 1-(4-methoxyphenyl)-2-aminopropane. PMA is a methoxylated amphetamine derivative. Precursors and reagents include 4-methoxybenzaldehyde, nitro-ethane, benzene, methanol and cyclohexane.

Precursors for PMA and PMMA are widely available commercially. PMMA and PMA themselves have no therapeutic value.

In general, colour tests for PMMA and PMA are presumptive and need confirmation. Limited data have indicated that, with regard to the reaction of PMA and PMMA to colour change tests, two samples analysed by gas chromatography–mass spectrometry (GC–MS) which identified PMA and PMMA, produced no reaction in the Marquis colour test. They gave a positive result for the nitroprusside colour test and a colour change of purple to brown for the Liebermann colour test. PMMA produces the positive blue colour of a secondary amine, while PMA does not elicit a colour. Additional complications arise with colour tests performed on tablets that contain mixtures of different amphetamine analogues.

Pharmaceutical description

PMMA/PMA have been sold as tablets for oral consumption. They are sold in the guise of MDMA with 'ecstasy' type logos such as 'Mitsubishi', 'Jumbo' or 'E'.

Health risks

Individual health risks

Acute effects

A recent animal study indicated that PMMA induces awakening and stimulant effects. In discrimination studies, in MDMA-trained rats, PMMA is considered to be identical to MDMA. In PMMA-trained rats, MDMA is considered to be identical to PMMA, but this is not the case for amphetamine or the hallucinogen 4-methyl-2,5-dimethoxyamphetamine (DOM). Lacking hallucinogenic properties, PMMA may have mostly 'entactogenic' effects, meaning that it enhances introspective states, while PMA has some amphetamine-like characteristics.

Pharmacokinetic experiments with five amphetamine-like stimulants revealed a poor penetration of PMA into the brain. Comparisons of the brain levels of these amphetamines suggested that PMMA crosses the brain barrier to a lesser extent even than PMA.

Neurochemical effects of PMMA have not been investigated in *in vitro* studies. Structure-activity investigations on the neurotoxic effects of amphetamine derivatives suggested that PMMA is a serotonin (5-hydroxytryptamine, 5-HT) releaser, yielding potent and selective effects on serotonergic neurones. Repeated administration of PMMA (or PMA) in rats for four days produced a brain depletion of serotonergic markers. The results of recent animal experiments in rats and mice have confirmed previous studies which found some symptoms indicative of 'serotonergic syndrome', although some symptoms (e.g. short-term respiratory depression) were not found.

The neuronal basis for the hyperactivity and sympathomimetic stimulation observed with PMMA is still unclear. Unlike MDMA, PMA and PMMA do not seem to release dopamine. From its chemical structure, it is likely that PMMA plays a dominant role in the inhibition of monoamineoxidase (MAO)-A. *In vitro* experiments demonstrated that PMA is a potent inhibitor of MAO. As is the case for PMA, the phenylisopropylamine PMMA is probably also metabolised by the cytochrome isoenzyme P450 2D6. It can be concluded from these findings that the acute effects of PMA (and probably PMMA) are more likely to be associated with alterations in serotonergic rather than in dopaminergic neurotransmission.

With PMMA administration in rats, hypertension and long-lasting tachycardia are observed; these cardiovascular effects are dose dependent. MAO inhibition may contribute to the long-lasting cardiovascular effects.

The main acute toxicity effect of PMMA in rats is hyperthermia. This effect occurs soon after PMMA administration and before the onset of hyperactivity. Hyperthermic responses are dose dependent.

From experiments in animals, it may be assumed that PMMA is an effective psychoactive substance with toxic effects. The median subcutaneous lethal dose value (LD_{50}) of PMMA was found to be 80–100 mg/kg in rats. This value suggests a narrow

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

margin between the behaviourally active dose and the lethal dose and therefore there is a high risk for acute toxicity. PMA has a similar toxicity (LD_{50}) to PMMA in mice.

Standard toxicity data on the teratogenic, mutagenic and carcinogenic potential of PMMA are lacking. In general, arrangements should be made for the provision of standard reference materials and associated analytical data to forensic and toxicology laboratories in the EU.

Clinical effects

Tablets containing PMMA alone, marketed as 'ecstasy', were associated with one death which took place in Spain in 1993. Due to the presence of significant concentrations of 3,4-methylenedioxy-N-ethylamphetamine (MDEA) and ethanol in the blood sample, forensic experts considered that the role of PMMA in this death was problematic.

During a recent episode of seizures of PMMA in combination with PMA in the EU, there appeared to be some tablets in which PMMA was the principal substance (e.g. 97 mg PMMA combined with 4 mg PMA in one tablet). In most cases, PMMA was found in combination with PMA and other drugs such as methylenedioxyamphetamine (MDA), MDMA, amphetamine, methamphetamine and ephedrine.

PMMA/PMA have been involved in four deaths in the EU between July and September 2000 — one took place in Austria (*) and three in Denmark.

PMA alone has been implicated in six deaths in the Member States since June 2000: two in Germany in 2000 and four in Belgium in 2001. Hyperthermia (ranging between 41.5 and 46.1 °C) was a recurrent symptom in a number of documented cases of PMA-related fatalities.

Repeated intake of PMA or PMMA may cause inhibition of the isoenzyme responsible for its metabolism in the liver and could consequently enhance the hyperthermic response. High ambient temperatures and water deprivation also augmented the hyperthermia. The acute toxicity of PMA and PMMA may be due to increased extraneuronal serotonin levels.

(*) It has been confirmed that the cause of the fatality which occurred in Austria, which was allegedly associated only with PMA, was in fact due to PMA and PMMA.

In the human cases of fatalities, blood concentrations of PMMA were within the same range as the blood concentrations of PMA or MDMA in the case of deaths.

Monitoring the area under the plasma concentration–time curve (AUC), the findings in rats were that the maximum effects of PMMA and MDMA occurred 15 minutes after their administration. This may be relevant when analysing causes of overdose leading to human fatalities. The risk of overdose could be linked to the fact that, after receiving only a weak stimulant effect, the lack of the expected MDMA-like properties may lead users to take more tablets in the belief that this initial dose was too low.

The combination of PMA and PMMA, as well as the combination of PMMA with other amphetamines, increases toxicity and may present an additional risk factor in the case of overdose.

As with MDMA, there is some concern that PMMA and PMA could induce degeneration of serotonergic neurones.

Dependence

Drug discrimination learning for PMMA has only been studied in animals. Low doses of PMMA (1.25 mg/kg) have a discriminative stimulus similar to that induced by 'entactogen' substances such as MDMA. There have been no systematic studies of the potential for PMMA dependence in animals or in humans. The lack of dopamine effects would tend to indicate a low dependence potential because of the central reinforcing role of dopamine release. In contrast with MDMA effects, reports from users indicate reduced motivation to talk and to get involved with others, and undesired physical effects. It is unlikely that, in the long term, fake 'ecstasy' tablets combining PMMA and PMA could replace MDMA on the retail market.

Psychological effects

There are few data on the neuropsychological effects of PMMA in humans. Limited animal data suggest effects similar to the 'entactogen' class, which are different to amphetamine-type stimulants and to hallucinogenic (LSD) effects. Anecdotal reports from 'ecstasy' users, although not entirely consistent, indicate that it frequently produces more unpleasant effects than 'ecstasy'.

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

Public health risks

Availability and quality

There appears to be no explicit consumer market in the EU for either PMA or PMMA. PMMA is sold on the illicit market as a substitute for 'ecstasy'. The combination of PMMA with PMA in tablets sold with an 'ecstasy'-type logo does not seem to be accidental but more probably is a deliberate association of the two compounds, whose behavioural effects have been described in the existing literature, in order to imitate the expected effects of MDMA as closely as possible for users. The widespread availability of the precursors implicated in the synthesis of both PMMA and PMA may have enhanced this process.

Since June 2000, four Member States (Denmark, Germany, Austria and Sweden) have reported a total of nine large seizures of PMMA/PMA tablets sold as 'ecstasy'. The Netherlands reported three large seizures of tablets containing PMA together with MDMA or MDA, and two seizures of tablets containing PMA alone. A significant number of small seizures of 'ecstasy' tablets containing PMA and/or PMMA have been reported in eight Member States (Sweden, France, Germany, the Netherlands, Belgium, Austria, the United Kingdom and Spain) as well as in Norway and Poland. Large PMA and/or PMMA seizures have also been reported in Hungary and Canada.

The most common logos found on tablets containing PMMA/PMA are 'Mitsubishi', 'Jumbo' or 'E'. In one seizure, a tablet with a four-leafed clover logo was found. Other tablets containing PMA (but no PMMA) have carried 'Mitsubishi', 'Elephant', 'Nike', 'Superman', and 'xTc' logos.

PMMA has always been found in combination with PMA in tablets sold as 'ecstasy' ⁽⁵⁾. Most PMMA/PMA tablets also contain a mixture of amphetamine, methamphetamine or ephedrine. On the basis of the available information, tablets contain between 20 and 97 mg PMMA.

⁽⁵⁾ With the exception of Spain where, between August and October 2000, three seizures took place of a small number of tablets which contained PMMA but no other identifiable drug contents.

Knowledge, perceptions and availability of information

There is considerably more scientific information about PMA than about PMMA. Specific information about the dangers of PMA is available in a variety of forms including peer education, outreach work, leaflets, youth media, television, newspapers and the Internet. Furthermore, the availability of 'ecstasy' testing kits sold commercially on the Internet indicates a demand for better knowledge about the contents of tablets, although this demand may be largely from dealers.

There is no information about the knowledge or the perceptions of users of PMMA, used alone or when combined with PMA, as there is no market for PMMA/PMA as such.

Prevalence and patterns of use

The prevalence of the (inadvertent) use of PMMA depends on the extent to which, as is currently the case, it is sold as 'ecstasy'. However, PMMA is believed to form only a very small proportion of the 'ecstasy' market. Patterns of use are the same as for 'ecstasy', a situation which could be a matter of serious concern as users may seek similar effects to MDMA. In that regard, the combination of PMA with PMMA represents a major risk.

Characteristics and behaviours of users

Evidence suggests that age and where people live have more influence than gender on 'ecstasy' use, and therefore on inadvertent PMMA/PMA use. However, there is anecdotal evidence that males are more likely to use 'ecstasy' excessively and to be less concerned about the harmful effects than female users.

Special concerns are the lack of knowledge both about drug contents and about the specific harmful effects of PMA and PMMA. The greatest risk behaviour associated with use is taking large doses of PMMA/PMA as if it were MDMA. People who take more than one tablet over a short time period are at the greatest risk of both acute and long-term health risks. One group of young people who are particularly vulnerable are heavy, excessive users who belong to groups that are at high risk for a range of problems.

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

Indicators of health consequences

In Spain, there was a death associated with the use of PMMA alone, in 1993, and another fatality with PMA in 1995. Since 1995, PMA has been implicated in at least eight deaths in Australia and in 10 in the United States (USA).

Since July 2000, four deaths have been recorded as being linked to PMMA/PMA: one in Austria and three in Denmark. A further six deaths have been linked to PMA alone in two other Member States: two in Germany and four in Belgium. In at least five out of the nine deaths, more than one tablet had been taken. In one case, at least six other drugs had also been taken. PMA was also suspected to be involved in the recent death of a young man in the Netherlands.

Four non-fatal hospital admissions associated with PMA have been reported in Belgium since April 2001.

It should be noted that increased investigations for PMA may have been prompted by a heightened awareness of the potential role of PMA in 'ecstasy' intoxication.

Context of use

PMMA is taken in the context of an 'ecstasy' culture in which prior expectations exist with regard to the quality and the timing of effects. Consequently, the poor MDMA-like effects of PMMA, even when combined with PMA, may be perceived as a weakness or failure of the pill taken in the belief that it is 'ecstasy'. This may lead to the consumption of more pills and subsequent overdose.

Social risks

Sociological aspects

Sociological evidence for PMMA and PMA is limited by the fact that there is no evident consumer market for these drugs in Europe. In the cases where PMMA has appeared on the European market, it has always been consumed with PMA in a tablet which was taken as 'ecstasy' and where the user expected to experience MDMA effects accordingly.

Social consequences

There is no specific evidence on PMMA. The available evidence on MDMA does not show any major harmful social consequences, for users, arising directly from its use, in terms of family or other social relations, problems concerning education, employment, or marginalisation.

The recent deaths that have occurred from PMMA/PMA or from PMA alone contribute to growing concerns about dangerous products on the 'ecstasy' market. These concerns are reflected in some Internet discussions where an interest in health issues and avoiding harm from new synthetic drugs is evident.

Consequences for the social behaviour of the user

There is no evidence to specifically link the effects of PMMA use with disorderly conduct, acquisitive crime or violence. Its effect on driving is unknown, but the narrow safety margin between the behavioural and the lethal doses may be a matter of concern.

Other social consequences

There is no indication that PMMA in particular is associated with any major value conflicts or has any important implications for social institutions beyond those described for MDMA.

Criminological aspects

Distribution of PMA is known to have taken place in six Member States: Belgium, France, Germany, the Netherlands, Sweden and the United Kingdom. This relates to the seizure of some 5 480 tablets in 19 incidents. Trafficking and distribution of PMMA is known to have taken place in four Member States: Denmark, Germany, Austria and Sweden.

In those cases where PMMA was seized — 18 870 tablets in 29 incidents — all tablets also contained PMA and had either the 'Mitsubishi' logo or the 'E' logo, with the exception of 337 tablets with the 'Jumbo' logo. The total number of PMA and PMMA/PMA tablets seized in the Member States in 2000 is relatively small when compared to the overall seizures of 'ecstasy' in the EU (17 426 531 tablets in 2000). Large-scale production of PMA or PMMA is not thought to occur in any Member State.

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

Three Member States — Denmark, Austria and Sweden — have information on the role of organised crime in the trafficking of PMMA/PMA. This relates to criminal groups from Poland. Combined with links established by the Bundeskriminalamt (BKA), and the fact that the Polish authorities have discovered two illicit laboratories used for the production of PMA and PMMA, this indicates that PMMA/PMA tablets seized in the Member States, Canada and the USA, are likely to have originated in Poland. According to the Polish authorities, production of PMA and/or PMMA continues to take place in other laboratories in the country and in the Ukraine.

Seizures of PMMA/PMA tablets in 2001 in the Member States probably relate to importation from Poland in 2000.

Prohibition

Legal status

An analysis of the legal status of PMMA in the 15 Member States shows that the drug is controlled under the national drugs legislation in four of them: Germany, Ireland, Sweden and the UK. PMMA is also controlled in Norway. Steps are being taken in France to schedule PMMA control under its national drugs legislation. In addition, an assessment on PMMA/PMA has recently been conducted by the Coordination Centre for Assessment and Monitoring of New Drugs of Misuse (CAM) in the Netherlands.

PMA has been listed as a controlled drug in Schedule I of the 1971 UN Convention on Psychotropic Substances since 1986.

Possible consequences of prohibition

The meeting acknowledged the well established and broadly accepted fact of prohibition of MDMA. As this substance served as a point of reference for the risk assessment of PMMA, and in view of the fact that the acute hazards of PMMA were generally not considered to be any less serious, there was strong support at the meeting that prohibition is the most appropriate measure of control. Another point of view expressed at the meeting was that PMMA cannot be regarded as a major public health problem for the time being.

In accepting prohibition of PMMA as the most applicable model of control, there was a strong consensus that prohibition should not impede any kind of non-repressive preventive or harm-reducing actions. Most importantly, an urgent need for educating and informing potential user groups of the hazards of the substance was expressed by the meeting to prevent them from inadvertently taking overdoses.

The meeting noted that, since PMMA is part of the larger 'ecstasy' market, prohibition is unlikely to have a significant impact on the availability and usage of 'ecstasy' in general. Nevertheless, prohibition in all Member States will facilitate international law enforcement and judicial cooperation against producers and traffickers of PMMA.

Conclusions

The Scientific Committee of the EMCDDA, extended with experts from the Member States and representatives of the Commission, Europol and the EMEA, has considered the health and social risks as well as the possible consequences of prohibition of PMMA alone and also when associated in 'ecstasy'-like tablets in combination with the controlled drug PMA. In accordance with Article 4 of the joint action, it submits the following conclusions:

- PMMA has no therapeutic value.
- The scientific evidence submitted to the meeting shows that PMMA is a psychoactive agent which seems to release serotonin and may inhibit MAO-A activity. In combination with PMA, it has been associated with four deaths within the EU. The reported adverse events are noteworthy in that they occur within a short period of time and in an apparently small population exposed to the drug. The simultaneity of a weak, MDMA-like, stimulant effect and a lack of other anticipated effects apparently increases the risk of overdose. Combination with alcohol, MDMA, amphetamines or ephedrine may increase the risks of neurotoxicity.

The expert participants noted that PMMA had been identified in four Member States and also in Norway, Poland, Canada and the USA. Three of these Member States have identified a role for organised crime in the trafficking of PMMA. PMMA is almost exclusively sold in combination with PMA and is consumed as 'ecstasy'. Anecdotal reports suggest that PMMA/PMA tablets may be less attractive than MDMA to users because of their unpleasant effects.

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

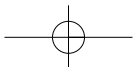
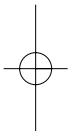
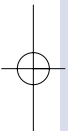
Compared to MDMA, PMMA, especially when associated with PMA in 'ecstasy'-like tablets, appears to be associated with a higher risk of acute effects including adverse reactions and overdose. The meeting also recognised gaps in knowledge. Further studies should be conducted to establish the exact role of PMMA in these toxic effects.

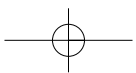
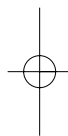
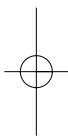
- As a consequence of the previous two points, because PMMA is an amphetamine analogue that is very similar to PMA, and also because both MDMA and PMA are subject to control in all Member States, the opinion which received strong support at the meeting was that this compound should be placed under control.

This opinion also recommended that a decision to place PMMA under control should not inhibit the gathering of information about drugs on the market or the dissemination of accurate information about PMMA and PMMA/PMA to users and relevant professionals. The risk of overdosing should be highlighted, as should the risks of consuming it with alcohol, MDMA, amphetamines and ephedrine products.

- The major chemical precursors of PMMA are available commercially. The meeting recommends that the Drug Precursors Committee, which was set up under Article 10 of Regulation (EEC) No 3677/90 and Directive 92/109/EEC, should be invited to closely examine the specific precursor chemicals which have been found to be used in the manufacture of PMMA and which are not yet subject to any measure of surveillance.
- The meeting reiterates its previous risk assessment recommendations that, when a new synthetic drug is notified for risk assessment, arrangements be made for the provision of standard reference material and associated analytical data to forensic and toxicology laboratories within the EU. The meeting further recommends that PMMA be included in the UN Drug Control Programme (UNDCP) proficiency testing programme.

Lisbon, 29 October 2001





Chapter 2 Council decision

Council decision of 28 February 2002 concerning control measures and criminal sanctions in respect of the new synthetic drug PMMA ^(*)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on European Union,

Having regard to joint action 97/396/JHA of 16 June 1997 concerning the information exchange, risk assessment and the control of new synthetic drugs (?), and in particular Article 5(1) thereof,

Having regard to the initiative of the Commission,

Whereas:

(1) A risk assessment report on PMMA was drawn up, on the basis of Article 4(3) of joint action 97/396/JHA, at a meeting convened under the auspices of the Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction.

(2) At present, PMMA is controlled under the national drugs legislation in four Member States.

(3) PMMA is not currently listed in any of the schedules to the 1971 UN Convention on Psychotropic Substances. PMMA poses health risks for individuals and could pose a threat to public health. PMMA is an amphetamine analogue very close to PMA which is included in Schedule I to the 1971 UN Convention. PMMA has no therapeutic value.

(4) Within the EU, PMMA has always been consumed with PMA in tablets taken as 'ecstasy' (MDMA). There is no explicit consumer market for either PMMA or PMA.

(*) Council Decision 2002/188/JHA (OJ L 634, 6.3.2002, p.14).

(?) OJ L 167, 25.6.1997, p. 1.

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

(5) PMMA has been associated in combination with PMA with three deaths ⁽⁸⁾ within the European Community. Experiments on animals indicate that there is a narrow margin between the behaviourally active and lethal dose of PMMA and therefore a high risk of acute toxicity exists. PMMA seems to have a similar toxicity to PMA and MDMA.

(6) Trafficking and distribution of PMMA have taken place in four Member States and three of these have information on the role of organised crime in the trafficking of PMMA/PMA. In all 18 870 tablets containing PMMA have been seized in 29 incidents. Large-scale production of PMMA does not take place in the EU. Two laboratories have been seized in countries of eastern Europe and production is believed to continue there.

(7) PMMA should be subjected by the Member States to control measures and criminal penalties, as provided for under their legislation complying with their obligations under the 1971 UN Convention on Psychotropic Substances with respect to substances listed in Schedules I or II thereto,

HAS DECIDED AS FOLLOWS:

Article 1

Member States shall take the necessary measures, in accordance with their national law, to submit PMMA to control measures and criminal penalties, as provided for under their legislation complying with their obligations under the 1971 UN Convention on Psychotropic Substances with respect to substances listed in Schedules I or II thereto.

Article 2

Member States shall, in accordance with the third subparagraph of Article 5(1) of joint action 97/396/JHA, take the measures referred to in Article 1 within three months of the date on which this decision takes effect. Within six months of the date on which this decision takes effect, Member States shall inform the Secretariat General of the Council and the Commission of the measures they have taken.

⁽⁸⁾ The number of deaths has increased since this decision was drawn up.

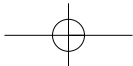
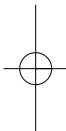
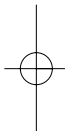
Chapter 2: Council decision

Article 3

This decision shall be published in the Official Journal. It shall take effect on the day following its publication.

Done at Brussels, 28 February 2002.

For the Council
The President
A. Acebes Paniagua



Chapter 3

Europol-EMCDDA progress report

Europol-EMCDDA progress report on PMMA and PMA ⁽⁹⁾ in accordance with Article 3 of the joint action of 16 June 1997 concerning the information exchange, risk assessment and control of new synthetic drugs

Introduction

PMMA is a non-scheduled, new synthetic drug which has been found in association with PMA in 'ecstasy'-like tablets. PMA has been listed in Schedule I of the 1971 UN Convention on Psychotropic Substances since 1986, and first appeared on the European market in December 1998. PMMA is regulated by law in four Member States: Germany (emergency scheduling List I of the Narcotics Act of 10 October 2000), Ireland (Schedule 1 of the Misuse of Drugs Acts, 1977 and 1981), Sweden (Ordinance SFS 1999:58) and the UK (Misuse of Drugs Act 1971, Class A).

PMA is a potent drug with amphetamine-like characteristics and is a potentially lethal substance. Found in 'ecstasy'-like tablets, alone or in combination with MDMA, it has been associated with a number of deaths in Australia and, in combination with MDMA or PMMA, in the USA during the period 1998-2000. In the EU since July 2000, PMA has been implicated in a number of deaths that have occurred after ingestion by drug users of PMA in the form of 'ecstasy'-like tablets, either alone (one case in Austria) or in combination with PMMA (four cases in Denmark and four cases in Germany) ⁽¹⁰⁾.

The association of PMMA/PMA became known to the authorities in the Member States in June 2000 when the Danish police arrested a man who was in possession of approximately 700 tablets with a 'Mitsubishi' logo, to be sold as 'ecstasy'. He told the police he had already sold 300 of these tablets. On 18 July 2000, in the framework

⁽⁹⁾ Europol file 2564-132.

⁽¹⁰⁾ Following a recent toxicological review of deaths in Spain, the Spanish Reitox national focal point informed us that PMMA was detected in one death in 1993 and PMA was detected in one in 1995.

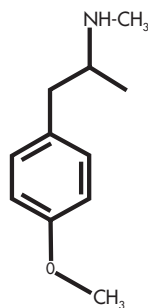
Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

of Article 3 of the joint action on the early-warning mechanism on new synthetic drugs, Europol transmitted information received from the Danish authorities to the EMCDDA regarding the death of two 20-year-old men on 2 and 5 July 2000 and the hospitalisation of two more young people after the intake of 'ecstasy'-like tablets with the 'Mitsubishi' logo. Laboratory analysis of the tablets that were found in the possession of the arrested man revealed that the tablets contained both PMA and PMMA. Based upon the autopsy findings, the forensic report stated that the presumed cause of the deaths in Denmark was acute intoxication with PMA and PMMA in one death, and with PMA, PMMA and MDMA in the other. The EMCDDA was later informed by the Danish Reitox national focal point about the death of a third, 24-year-old man on 2 September 2000 which, according to the final forensic report, was most probably caused by acute intoxication with PMA and PMMA.

Available information on PMMA and PMA

Chemical and physical description, including the names under which PMMA and PMA are known

Figure 1: Chemical structure of PMMA

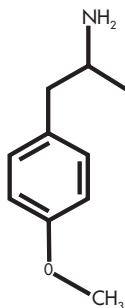


The molecular formula of PMMA is $C_{11}H_{17}NO$. Known as 4-methoxymethyl-amphetamine (4-MMA in Shulgin's Pihkal (Shulgin, 1991)) or by the acronym PMMA, its full chemical name is N-methyl-1-4-(methoxyphenyl)-2-aminopropane. PMMA is a structural hybrid of PMA and methamphetamine⁽¹⁾ (Figure 1). PMMA is commonly

⁽¹⁾ The ethyl analogue of PMA, N-ethyl-4-methoxyamphetamine, has been detected in a urine sample in Belgium.

encountered in the form of tablets. Street names for PMMA/PMA tablets in Austria are 'killer' and 'red Mitsubishi'. Tablets seized in Austria, Germany and Spain were white, red, beige or brown in colour, and marked with 'E' or 'Mitsubishi'.

Figure 2: Chemical structure of PMA



The molecular formula of PMA is $C_{10}H_{15}NO$. Known as 4-methoxyamphetamine (4-MA) or by the acronym PMA, its full chemical name is 1-(4-methoxyphenyl)-2-aminopropane. PMA is a methoxylated amphetamine derivative (Figure 2).

From 1972 to 1973, PMA was sold in the USA and Canada in powder form, sometimes in capsules, under the street names 'Chicken yellow', and 'Chicken powder', and often sold as MDA. Since the mid-1990s, PMA in 'ecstasy'-like tablets has been believed by users to be MDMA. PMA has been encountered in the EU in powder and tablet form. Reported street names in Austria are 'Death' and 'Red Mitsubishi', and 'Mitsubishi double-stack' in the USA. Tablets seized in France and the UK were white or beige in colour, marked with 'Superman' or 'Elephant'.

The frequency, circumstances and/or quantities in which PMA/PMMA is encountered

Information received by the EMCDDA

Nine EU Member States (Belgium, Denmark, Germany, Spain, France, the Netherlands, Austria, Sweden and the UK) have reported seizures of PMA or PMA/PMMA and/or have encountered these substances in toxicological tests (Belgium, Spain, Austria) or in pill-testing programmes (e.g. the 'Check-it!' programme in Vienna).

Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs

In July 2000, the Austrian Reitox national focal point reported on the death of a 17-year-old man. Forensic analysis confirmed that PMA was involved in his death. Austrian police investigations relating to this death led to the seizure of 4 478 tablets of PMA, all with the 'Mitsubishi' logo. The colour of 1 785 of these tablets was white and 2 693 were red-brown. On 16 September 2000, PMA/PMMA was found for the first time during a 'Check It!' pill test at a rave party in Vienna. After the analysis of 48 tablets being sold as 'ecstasy', four were found to contain 400 mg of PMA in combination with PMMA and amphetamine. The tablets were red in colour, had the 'Mitsubishi' logo, and were 7 mm in diameter and 5 mm thick. They weighed 230 mg each and had a cylindrical shape. On 7 October 2000, the EMCDDA was informed of the detection of another PMMA/PMA tablet found at a rave party in Vienna by 'Check-it!' testing. The logo was a very deep stamped 'E'. The tablet was white and had the same physical characteristics, in terms of shape, diameter, thickness and weight, as the tablets analysed in September. The tablet contained 40 mg of PMMA and 20 mg of PMA, with small amounts of amphetamine or ephedrine. All tablets detected in Austria were sold as 'ecstasy'.

The Danish Reitox national focal point reported three deaths associated with PMA/PMMA, which occurred between 2 July and 2 September 2000. In Denmark, tablets seized in July 2000 were marked with the 'Mitsubishi' logo, were light brown in colour, 7 mm in diameter, weighed 280 mg and did not have a break line. Between 29 June 2000 and 7 March 2001, there were 16 more seizures of a total of 1 384 PMA/PMMA tablets. The largest seizure consisted of 843 tablets, which were seized in Copenhagen on 15 January 2001. According to laboratory findings, tablets in 14 of the 16 seizures were beige in colour, marked with the 'Mitsubishi' logo and were 7 mm in diameter, 5.1 mm thick and 230 mg in weight, on average. Five tablets contained ephedrine in addition to PMA and PMMA. In the other two seizures, the tablets seized were white with an undefined logo and weighed 88 and 139 mg, respectively.

At the beginning of July 2000, Europol received information from the BKA about three tablets seized in Friesland in northern Germany containing PMMA/PMA. The same information was transmitted to the EMCDDA by the German Reitox national focal point using a Europol-EMCDDA reporting form for new synthetic drugs. The tablets carried the 'Mitsubishi' logo, were 7.2 mm in diameter, 5.1 mm thick, weighing 220 mg with a break line on the back. Europol reported one death after the

use of such a tablet. One year before, in July 1999, an illicit laboratory had been dismantled in Brandenburg, Germany, where small amounts (<10 g) of PMA and PMMA were discovered. The German Reitox national focal point reported that PMA was also suspected of being involved in the death of an 18-year-old woman in November 2000, according to the *Land* criminal police office (LKA) of Rhineland-Pfalz.

The French Reitox national focal point reported on the results of toxicological analyses which demonstrated the presence of PMA in samples (five tablets, two powders). The samples were encountered in February 2001 in the Aquitaine region in the south-west of France and in Bourgogne, Champagne and Franche-Comté in the east of France. This was the first time that PMA was identified within the French *Système national d'identification des toxiques et substances* (Sintes) system. Tablets had the 'Superman' logo, were white or beige, scored, 8.1 mm in diameter, 4.9–5.0 mm thick and weighed 299–308.8 mg. They contained PMA in combination with either MDMA, MDA or DMA (dimethoxyamphetamine). The powders were white and contained PMA, chloroquine and MDA.

The Spanish Reitox national focal point reported that tablets without logos containing PMMA had been analysed in 2000: six brown tablets with PMMA, caffeine and procaine in Tarragona, Cataluña on 28 August 2000, five brown tablets with PMMA in San Sebastian on 22 September 2000, and a number of white tablets with PMMA and caffeine in Tarragona on 13 October 2000.

The Belgian Reitox national focal point reported on a non-fatal emergency in April 2001 when PMA, together with MDMA and MDA, was detected in the urine sample of a 17-year-old girl brought to the emergency care unit.

The Swedish Reitox national focal point notified that there were two seizures of PMA in 1998⁽¹²⁾ and four seizures of PMA/PMMA as well as three seizures of PMA between March and November 2000. The largest seizure took place in Stockholm on 9 November 2000 and consisted of 1 782 PMA/PMMA tablets. Amphetamine and methamphetamine were also found in some of the other seizures.

⁽¹²⁾ On 23 December 1998, two seizures of PMA were notified by the Europol national unit in Sweden using the reporting form for new synthetic drugs.

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The United Kingdom Reitox national focal point reported on the seizure of 14 white PMA tablets (8.1 mm by 4.7 mm, weighing 295 mg) in Leicestershire on 16 November 2000. Analysis by the Birmingham laboratory of the forensic science services revealed that they each contained 31 mg of PMA and 20 mg of MDMA, as well as caffeine. The tablets were marked with an 'elephant' logo facing right on the flat surface opposite a half-scored convex face. They were identical to tablets identified in the Netherlands in late 2000.

The Dutch Reitox national focal point informed on the seizure of 119 tablets in 2000, containing PMA, MDMA and traces of MDEA and caffeine. In the *Drugs Informatie en Monitoring Systeem* (DIMS) report 1998–2000, it was indicated that two tablets containing PMA/PMMA were detected by the DIMS system in 2000.

Information received by Europol

The Europol national units of Austria, Denmark, Germany, the Netherlands and Sweden have reported seizures of tablets containing PMMA, with or without PMA, to Europol. The reported seizures are mentioned in Table 1. In addition, the German BKA provided reports of seizures of PMMA/PMA in France. Nine Member States (Belgium, Greece, Spain, Ireland, Italy, Luxembourg, Portugal, Finland and the UK) have reported that, as yet, they have not seized any PMA and/or PMMA.

Table 1: Overview of seizures of PMA/PMMA in the Member States as reported to Europol (until March 2001)

Member State	Number of tablets	Logo	Active substance		
			PMA	PMMA	Other
Austria	1	'E'	*	*	
	4–5	'Mitsubishi'	*	*	
	1 785	'Mitsubishi'	*	*	Amphetamine
	2 693	'Mitsubishi'	*	*	
	10 000	'E'	*	*	
Denmark	1–2	'Mitsubishi'	*	*	
	1	'Mitsubishi'	*	*	
	1	'Mitsubishi'	*	*	
	4	'Mitsubishi'	*	*	
	68	'Mitsubishi'	*	*	

Member State	Number of tablets	Logo	Active substance		
			PMA	PMMA	Other
	78	'Mitsubishi'	*	*	
	83	'Mitsubishi'	*	*	
	155	'Mitsubishi'	*	*	
	718	'Mitsubishi'	*	*	
	843	'Mitsubishi'	*	*	
France	1 (°)	No logo	*		MDA and chloroquine
	1 (°)	No logo	*		MDA and chloroquine
	1 (°)	'Superman'	*		MDMA
	1 (°)	'Superman'	*		MDMA
	1 (°)	'Superman'	*		MDMA
	1 (°)	'Superman'	*		MDMA
	1 (°)	'Superman'	*		DMA
Germany	3	'Mitsubishi'	*	*	Ephedrine
	5	'Mitsubishi'	*	*	Ephedrine
	10	'Mitsubishi'	*	*	Ephedrine
	18	'Elephant'	*		MDMA
	8	'Elephant'	*		MDMA
Netherlands	17	'Mitsubishi'	*	*	
	27	'Elephant'	*		
	119	'Elephant'	*		
Sweden	5 000	'Elephant'	*		
	1	'Mitsubishi'	*	*	Amphetamine
	1	'Mitsubishi'	*		Methamphetamine — amphetamine
	2	'Mitsubishi'	*		
	2	'Mitsubishi'	*	*	Amphetamine
	3	'Mitsubishi'	*	*	
	4	'Mitsubishi'	*	*	Methamphetamine
	8	'Mitsubishi'	*	*	
	19	'Mitsubishi'	*	*	
1 782	'Mitsubishi'	*	*		

(°) = sample only; the exact size of the seizure was not reported.

Source: Europol-EMCDDA progress report (2564-132).

The Austrian National Europol Unit reported the seizure of 4 478 tablets with the 'Mitsubishi' logo containing the active substances PMA and PMMA. These tablets were part of a 5 000 tablet shipment from a Polish citizen. A further 10 000 tablet shipment was planned for September 2000. On 17 October 2000, a Polish citizen was arrested after supplying 10 000 tablets with the 'E' logo containing the active substance PMA/PMMA. These tablets were smuggled by car from Poland to Austria.

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The Danish National Europol Unit reported 10 seizures of tablets containing PMA/PMMA. The size of the seizures varied between 1 and 718 tablets.

The German BKA reported six seizures of tablets containing PMA as the active substance. The BKA stated that four of the six seizures were made after a user died after taking one or more tablets and that, on 7 November 2000, another victim died after taking five tablets. Further investigation led to the arrest of a supplier in possession of 18 tablets containing PMA and MDMA as active substances, in addition to 974 'ecstasy' tablets, 100 LSD trips, 10 g of amphetamine and 7 g of herbal cannabis. The 18 PMA/MDMA tablets seized were part of a delivery of 1 000 tablets bearing the logo 'Mitsubishi'. In addition, the BKA reported information from the French Observatoire Français des drogues et des toxicomanies (OFDT) to Europol. The OFDT reported the results of the analyses of seven samples (five tablets with the logo 'Superman', and two powders) from seven investigations. PMA was detected in all the samples, MDMA in two and DMA in five of the samples.

Investigations by the BKA established that there was a relationship between the seizures in Austria, Denmark, Germany and Poland. The Polish authorities raided two illicit laboratories in December 2000, resulting in the arrest of four people. Inside these two laboratories, equipment, including two tableting machines, and chemicals were found. Further investigations demonstrated no relationship between the seized tablets and the two tableting machines. According to information from the Polish authorities, production of PMA and/or PMMA continues to take place in Poland. Further BKA investigations showed that tablets seized in Austria, Denmark Germany and , with the logo 'Mitsubishi' and 'E', were all from the same source.

The Dutch unit for synthetic drugs reported the seizure of 119 tablets containing PMA, bearing the logo 'Elephant', on 25 October 2000. After an exchange of information with the German authorities, in January 2001 the Dutch authorities seized a further 5 000 tablets, also with the logo 'Elephant' and containing PMA and MDMA. According to a report from the German BKA, there was no forensic link between the tablets with the 'Elephant' logo and the 'Mitsubishi' tablets that were seized.

The Swedish National Europol Unit reported a total of nine seizures of PMA in 2000. In eight of the cases, the quantities seized were limited, varying between 1 and 19 tablets

per incident. In one case, however, 1 782 PMA tablets were seized. PMMA was also detected in seven of the cases and, in addition, traces of amphetamine and/or methamphetamine were present in four of the cases.

The results of investigations by the Drugs Enforcement Administration (DEA) in the USA were compared with details of seizures (logos 'Mitsubishi' and 'E') in the EU, which demonstrated that tablets seized in the USA came from the same source as tablets seized in Denmark. Similar tablets seized in Canada are also suspected to be from the same source. According to the BKA, there is a high probability that all tablets with PMA/PMMA plus the logo 'Mitsubishi' and 'E' seized worldwide come from the same source. Tablets with the logo 'Elephant' are thought to be from a different source.

In summary, seizures were made in six Member States of tablets carrying the logo 'Mitsubishi', 'Elephant', 'E' and/or 'Superman'. Almost all of the tablets with the 'Mitsubishi' or 'E' logo contained both PMA and PMMA. The trafficking of PMA/PMMA tablets has occurred in three Member States. There were no recorded PMA/PMMA tablet seizures reported in nine of the Member States.

Investigations undertaken by the German BKA proved a relationship between the seizures in Austria, Denmark, Germany and Poland. Further BKA investigations showed that all the tablets containing PMA/PMMA bearing the logo 'Mitsubishi' or 'E' that were seized in Austria, Denmark, Germany and the USA came from the same source.

With the exception of one laboratory discovered in Germany in 1999, where small amounts of PMA and PMMA were produced, no Member State has any information regarding the production of PMA and/or PMMA in the EU. Two illicit laboratories have been detected and dismantled in Poland. The number of seizures during the period 2000–01, in particular in Denmark, however, suggest the involvement of organised crime in the production and trafficking of PMA and PMA/PMMA tablets sold as 'ecstasy'.

A first indication of the possible risks associated with PMA/PMMA

Taking into account the fact that PMMA was found in combination with PMA in almost all cases, it seems necessary to consider the possible risks of using these substances separately as well as when associated together in tablets sold as 'ecstasy'.

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PMA

In the EU, PMA has been involved in one death in Austria in July 2000. No clinical data are yet available on this case. There has also been a PMA-related death in Spain, in 1995.

There were a number of earlier cases in 1973 where PMA was involved in nine deaths in Ontario, Canada. At that time, PMA was not sold as 'ecstasy' but usually as MDA, in a powder form. Australian reports suggest that PMA has been involved in 11 to 12 deaths from 1997 onwards, sold as 'ecstasy'. PMA sold as 'ecstasy' has reappeared in Canada and in the USA, since February 2000. In the USA, several deaths were attributed to PMA in 2000 (Erowid web site, 2000).

A 50 mg PMA tablet induces a 'high' by increasing the pulse rate and blood pressure (BP) and by giving the user a feeling of well-being. Doses as low as 60 mg can cause significant increases in BP, body temperature and pulse. Larger doses can cause irregular heartbeats, heart attacks, breathing difficulty, kidney failure, convulsions, coma and death. Blood concentrations of more than 0.5 mg/l seemed likely to be associated with toxic effects. Death generally occurs when body temperatures rise so high that the central nervous system shuts down. The causes of death from PMA included documented hyperthermia in three cases (temperatures of 41.5–46.1 °C), with features of hyperthermia in one other case and intracranial haemorrhage in another.

In comparison with MDMA's immediate physiological response, PMA is known to have a delayed onset of action (around one hour). A possible consequence of this difference is that users may take several tablets of PMA when the expected effects are delayed or seem to be weaker than those of MDMA.

PMMA

There has been one PMMA-related death in Spain, in 1993. No other fatal or non-fatal emergencies involving PMMA alone have been reported to the EMCDDA or to Europol.

Discrimination studies on rats and mice have shown that PMMA lacks both amphetamine-like stimulant effects or hallucinogenic-like qualities but, being several times more potent than MDMA as a discriminative stimulus, it may be a prototypic

parent for the MDMA family of designer drugs (Glennon et al., 1988, 1997). In other studies, comparisons between the neurotoxicity potential of PMMA, PMA and MDMA suggest that PMMA, like PMA and MDMA, produces long-term (possibly neurotoxic) effects on brain neurones, but that PMMA is less potent than MDMA as a 5-HT neurotoxin (Steele et al, 1992).

PMA/PMMA

According to the German BKA, PMA and PMMA combinations have been involved in nine deaths in the EU: four in Germany, four in Denmark and one in Austria. The final forensic reports from Denmark confirmed that two of the deaths were probably caused by acute intoxication with PMA and PMMA and one death by acute intoxication with PMA, PMMA and MDMA. All victims were believed to have taken between two and five tablets bearing a 'Mitsubishi' logo, which were sold as 'ecstasy'.

According to the clinical reports, intoxication often resulted in an increase of body temperature (up to 41.5–46 °C) which, in the worse cases, will shut down the brain and vital organs, resulting in death.

Studies in pharmacology and biochemistry indicate that PMMA produces some of the MDMA-like effects that PMA is lacking, whereas PMA has somewhat amphetamine-like characteristics but no MDMA-like characteristics (Dal Cason, 2000). This feature may reinforce the first impression to users of having consumed a low dose of 'ecstasy'. This subjective effect, combined with the delayed onset of action of PMMA/PMA, may encourage some users to take multiple doses with a major risk of overdose.

One hypothesis about the PMA/PMMA association is that, by combining PMA and PMMA in fake 'ecstasy' tablets, illicit manufacturers selling the tablets aim to simulate the MDMA effects expected by users. It is also noteworthy that substituting PMA or PMA/PMMA for MDMA could be more cost-effective for illicit producers and may also present fewer risks. In fact, the precursors for PMA/PMMA are easier to obtain and less strictly controlled by legislation than those for MDMA.

Chemical precursors

The most recent synthesis of PMMA was performed by the DEA north central laboratory through catalytic hydrogenation of the precursor 4-methoxyphenylacetone (para-

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methoxyphenyl-2-propanone (PMP2P)). Other precursors and reagents quoted in Shulgin's *Pihkal* (Shulgin, 1991) are methylamine hydrochloride, sodium cyanoborohydride, ethyl chloroformate and formic acid.

Precursors for PMA ⁽¹³⁾ and PMMA are widely available commercially.

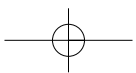
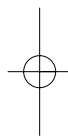
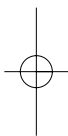
Mode and scope of established or expected use of PMA/PMMA as a psychotropic substance

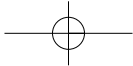
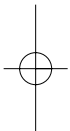
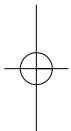
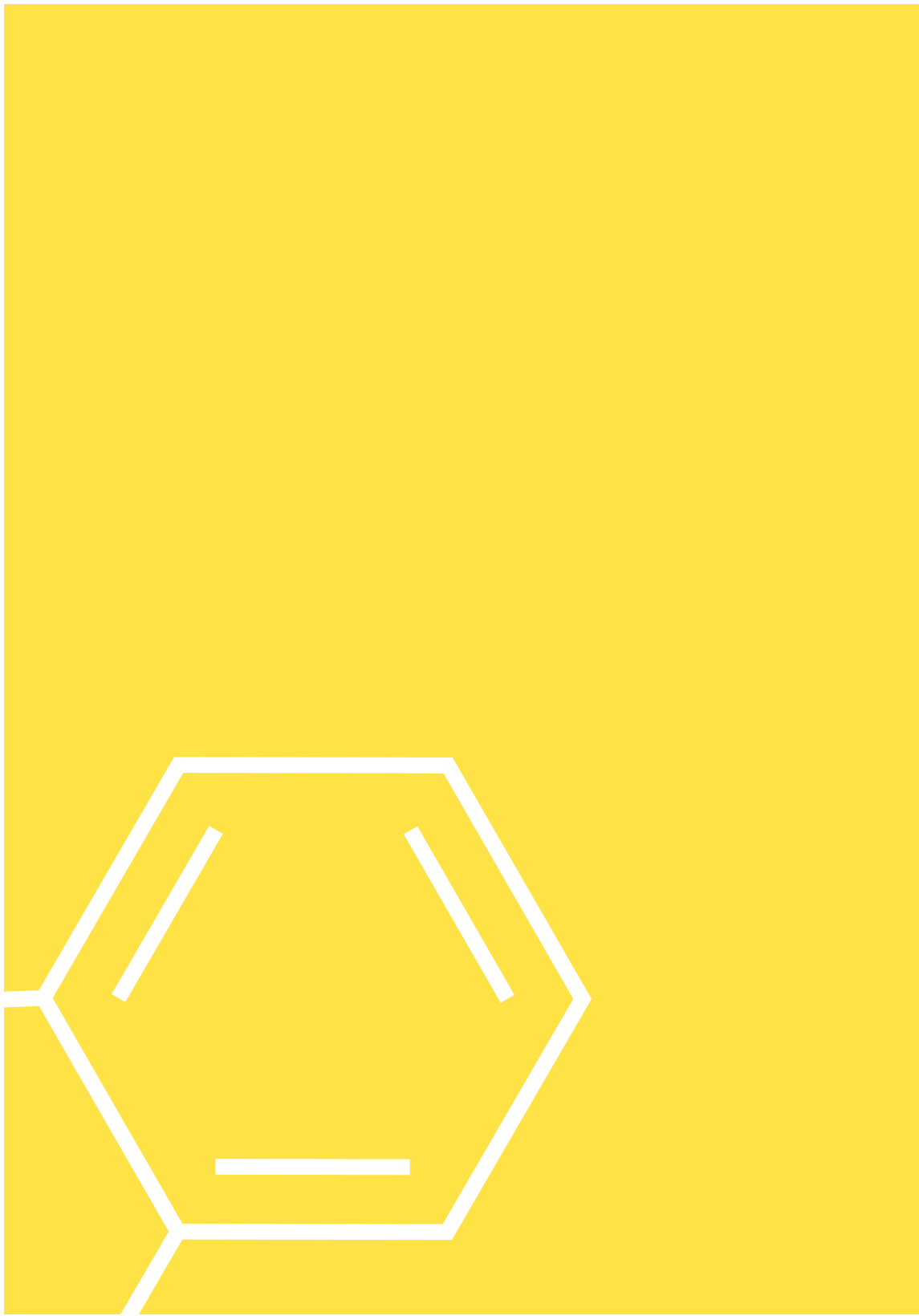
Illicit use of either is rare. Both are sold as MDMA. Several reports in the EU and the USA suggest that the 'rave' environment could be the main target for PMA/PMMA sold as 'ecstasy' by drug dealers. Users in France said that PMA tablets with the 'Superman' logo were usually easy to obtain. However, Internet sources imply a limited appeal for deliberate use of PMA and PMMA. Internet health warnings focus on the danger of relatively low doses of PMA or PMMA, especially when mistaken for 'ecstasy', and of more than 60 mg being consumed, according to 'ecstasy' patterns of use.

Other uses of PMA/PMMA and the extent of such use

There is no legitimate medical use of either PMA or PMMA.

⁽¹³⁾ PMA is available from Sigma Chemicals, catalogue No M 3404.





Chapter 4

Review of the pharmacotoxicological data on PMMA ⁽¹⁴⁾

Summary

Pharmacology and toxicology of PMMA in animals

- i. Drug discrimination experiments have demonstrated that PMMA lacks amphetamine-like or hallucinogenic properties. In MDMA-trained rats, PMMA could be substituted for MDMA. In PMMA-trained rats, MDMA could be substituted for PMMA. However, PMMA could not be substituted for amphetamine or the hallucinogen, DOM.
- ii. PMMA did not stimulate locomotor activity in rats at dosages of up to 30 mg/kg. However, sympathomimetic stimulation (e.g. salivation, piloerection, lacrimation, convulsions) was observed at doses of 40 and 80 mg/kg of PMMA and these same doses also stimulated locomotor activity in rats.
- iii. *In vivo* chronoamperometry was used to investigate the effects of PMA on dopaminergic and serotonergic neurones. PMA potently inhibited serotonin reuptake but not dopamine reuptake. PMMA was not investigated.
- iv. In rats, PMA produced bradycardia and lowered systolic and diastolic BP at 20 °C ambient temperature but these effects did not occur at 30 °C. PMMA was not investigated.
- v. Catalepsy was observed in cats and rats after administration of PMMA, suggesting reduced dopaminergic activity in the striatum of these animals.
- vi. The neurotoxicity of PMMA, PMA and MDMA was investigated in rats. In all, 80 mg/kg of PMMA or PMA and 20 mg/kg of MDMA were administered each day for four consecutive days. The levels of serotonin were determined in four brain regions one week after the last dose. With the exception of the striatum, the levels of serotonin were significantly lowered. However, the reduction in the hypothalamus did not reach significance when the experiment was repeated. The reduction in serotonin after administration of PMMA is shown in Table 2.

⁽¹⁴⁾ This report was written by Prof. Dr Hans Rommelspacher of the Free University of Berlin, Germany.

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Table 2: The percentage reduction of serotonin in various brain regions after administration of 80 mg/kg/day PMMA to rats for four days

Brain region	First experiment	Second experiment
Hippocampus	-30 %	-30 %
Frontal cortex	-30 %	-25 %
Hypothalamus	-55 %	-25 %
Striatum	-20 %	-15 %

The levels of dopamine were not reduced by PMMA. PMMA and PMA were considerably less neurotoxic than MDMA; 80 mg/kg PMMA or PMA was approximately as toxic as 20 mg/kg MDMA.

- vii. The LD₅₀ value of PMMA was 80–100 mg/kg in rats. This value, together with points ii, iii and viii, suggests a narrow margin for non-toxic effects and a high risk of acute toxicity.
- viii. Comparison of the limited data that are available suggests that the acute toxicity of PMMA is less than that of PMA.
- ix. Pharmacokinetic experiments with five amphetamines revealed a poor penetration of PMA into the brain. The concentration of PMA in rat brain at 3 hours was ~10 % that of MDMA after application of equivalent doses; PMMA was not investigated. Comparison of the brain concentrations of the amphetamines suggested that PMMA crosses the blood-brain barrier less easily than PMA due to a methylated nitrogen on the side-chain — the concentration of 3,4-methylenedioxyamphetamine was greater than that of 3,4-methylenedioxymethamphetamine, which was greater than that of 3,4-methylenedioxy-N-ethylamine.
- x. *In vitro* experiments demonstrated that PMA is a potent inhibitor of MAO-A. PMA is 20 times more potent than (+)amphetamine; PMMA was not investigated.
- xi. PMA, and probably PMMA, are metabolised by cytochrome P₄₅₀ 2D6, which may interfere with the inactivation of certain medicinal drugs, such as fluoxetine.

Human pharmacology and toxicology of PMMA

- i. The acute ingestion of PMMA by experienced drug users, as documented on the Internet (n = 5), and in Shulgin's report (Shulgin and Shulgin, 1991) did not result in consistent psychological effects. A dose of below 90 mg seemed to induce no central effects whereas a 90 mg dose in another subject elicited unusual audiostimulation. A dose of 110 mg in this subject induced stimulation lasting one hour, followed by reduced motivation to talk and to become involved with others, and a slowing of the sensation of time. Shulgin and Shulgin, reported none of the central effects of MDMA after administering 110 mg PMMA. A third subject found 100 mg PMMA to be mildly relaxing and euphoric. A dose of 150 mg caused severe physical ill effects. A single subject ingested 215 mg PMMA and found the experience very similar to taking MDMA. Several of the volunteers reported sedating effects with PMMA.
- ii. The acute physical effects were also found to be dose dependent. A dose of up to 50 mg caused a hyperreflexia-like status. Higher doses induced eye muscle disturbances of a nystagmus-like type. Some volunteers reported an increase of pulse rate and all reported muscle stiffness, such as jaw lockdown. Some reported nausea and, after some hours, head and stomach pains.
- iii. There are no reports on the metabolism of PMMA. Three volunteers ingested 5 mg of radiolabelled PMA. PMA was 85 to 100 % metabolised within 24 hours. Demethylation of the para-methoxy-group was the main metabolic process followed by side-chain oxidation. An individual with a genetic defect of the P₄₅₀2D6 cytochrome (its prevalence in Caucasians is ~ 9 %) metabolised PMA much more slowly.
- iv. There are no reports of psychological dependence on PMMA.
- v. An assessment of the risks associated with acute intoxication with PMMA is not possible due to a lack of data. There is a single report of a fatality in which PMMA, but no PMA, was detected in the blood. Other amphetamines (2 µg/ml MDEA, 0.3 µg/ml MDA) were detected in the blood sample, in addition to 1.51 µg/ml PMMA. The report concluded that the cocktail of several amphetamines caused the death. Extrapolations from animal experiments suggest that 400–500 mg of PMMA is extremely toxic, possibly lethal, in humans. Shulgin and Shulgin, estimated that 150 mg of PMA is toxic.

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Structure-activity investigations suggest that PMMA activates serotonergic neurones more selectively than PMA: N-methylation of the side-chain increases affinity to the neuronal serotonin transporter — methamphetamine's affinity is greater than that of amphetamine. The hyperthermia-rhabdomyolysis syndrome, which is reminiscent of serotonin syndrome in several aspects, with intravascular coagulopathy, hyperkalaemia, arrhythmia, convulsions, culminating in multiorgan failure, is presumably the cause of death following PMMA intoxication.

Conclusions

There is only limited information available about PMMA. More is known about PMA and even more has been published about MDMA. The literature regarding amphetamine, and several of its other derivatives, is extensive. Some of the conclusions in the present report are based on experiments and experiences with compounds structurally related to PMMA; this is indicated in the text.

PMMA is sold on the illicit market as a substitute for 'ecstasy'. Most tablets also contain PMA. The neuronal actions of PMMA differ from MDMA with respect to dopaminergic neurones and the stronger inhibition of the enzyme MAO-A by PMMA (concluded from the actions of PMA). The dopaminergic neurones are not activated by PMA nor presumably by PMMA. In contrast to these two compounds (which, together with 4-MTA, are exceptions within the amphetamine family), the acute psychostimulant effects of MDMA are mainly caused by the activation of dopaminergic mechanisms. Dopamine is inactivated by both MAO-A, a neuronal enzyme which inactivates 5-HT and noradrenaline, and MAO-B. Based on the strong inhibitory effect demonstrated by PMA on MAO-A, the stimulating effect of a high dose of PMMA (e.g. 215 mg) is probably caused by noradrenaline and not by dopamine.

Experienced users report that the central effects of PMMA are relatively weak compared with MDMA. In some users, a dose of 110 mg PMMA caused euphoric and stimulating effects whereas, in others, no MDMA-like psychological effects were reported. Cardiovascular and muscular effects, however, were present. The reason for the weak psychological effects might be that PMMA penetrates the blood-brain barrier poorly compared with other amphetamines, as demonstrated in animal experiments with PMA.

Thus, the user expects the psychotropic effects of the active substance of the tablet he/she has consumed but is frustrated. The user perceives the cardiovascular and muscular effects, which seem to indicate that the tablet did contain an active compound. Therefore, the user consumes more tablets seeking the familiar psychological effects of 'ecstasy'. The dose-effect curve with respect to the toxic actions of PMMA and PMA (which is also present in most of these tablets) is much steeper than that of MDMA. Thus, the risk for acute toxic effects is much greater in the case of PMMA/PMA than for MDMA.

The limited data available from animal experiments suggest that PMMA is less toxic than PMA. The reason could be that PMMA penetrates the blood-brain barrier less easily than PMA and that PMMA is possibly more selective for serotonergic neurones than PMA and certainly than MDMA. The neurotoxic risk after repeated intake of PMMA is less than that of MDMA, possibly due to the lack of the involvement of the dopaminergic system: there is some evidence that dopamine is involved in the neurotoxicity of MDMA.

We can only speculate as to why PMMA has been added to PMA tablets in recent years by illicit laboratories. The high risk of acute toxic effects with PMA has been known for 30 years. The chemists may have expected PMMA to cause similar central effects to PMA and 'ecstasy', because drug discrimination experiments have demonstrated that PMMA can be substituted for MDMA but not for amphetamine or the hallucinogen, DOM. Animal studies suggest an entactogen-like action for PMMA without the brain stimulating effects of MDMA. This pattern of effects would allow a reduction of the amount of PMA in the tablets. The experiences of human volunteers suggest that very high doses (e.g. 200 mg PMMA) are necessary to elicit MDMA-like effects, possibly due to poor penetration of the blood-brain barrier. However, high doses of PMMA cause very unpleasant physical effects, elicited by the peripheral actions of PMMA.

There is no relevant therapeutic potential for PMMA.

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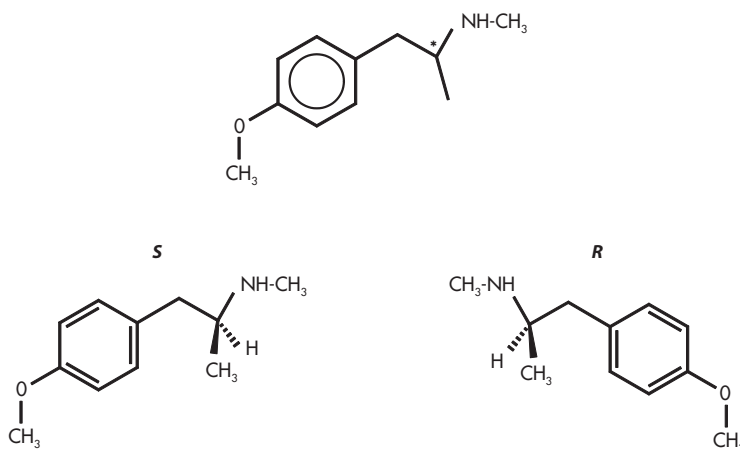
Chemical and pharmaceutical information

Chemical description

PMMA

PMMA was first synthesised in 1938 (Glennon et al., 1988). Its chemical name is 1-(4-methoxyphenyl)-2-methylaminopropane and its chemical formula is $C_{11}H_{17}NO$. It has a molecular weight of 179 (214.5 as hydrochloride) and a melting point of 177–178 °C. PMMA is also known as paramethoxy-N-methyl-amphetamine; N-methyl-1-4-(methoxyphenyl)-2-aminopropane; 4-methoxy-N-methyl-amphetamine (4-MMA); or 2-methylamino-1-(p-methoxyphenyl)-propane. Shulgin and Shulgin, (1991) described PMMA chemically as MDMA with one oxygen atom removed. Two optical isomers exist, S(+)-PMMA and R(-)-PMMA (Young et al., 1999) as shown in Figure 3.

Figure 3: PMMA has two optical isomers



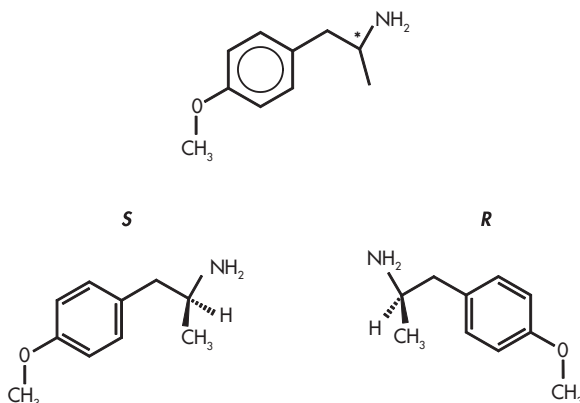
* Denotes chiral centre, R and S configuration for each optical isomer.

Precursor substances required for the synthesis of PMMA are: methylamine, 4-methoxyphenylacetone (4-methoxyphenyl-2-propanone) and cyanoborohydride. Additional substances required are: methanol, dichloromethane, isopropanol, hydrochloric acid, ethyl chloroformate, triethylamine, carbamate, formamide, lithium aluminium hydride. There is an alternative method of synthesis using PMA.

PMA

PMA's chemical name is 1-(4-methoxyphenyl)-2-aminopropane. Also known as 4-MA (4-methoxyamphetamine) or paramethoxyamphetamine, its chemical formula is $C_{10}H_{15}NO$. Its molecular weight is 165 (200.5 as hydrochloride) and it has a melting point of 206–207 °C. The chemical structure of PMA is shown in Figure 4.

Figure 4: PMA has two optical isomers



* Denotes chiral centre, R and S configuration for each optical isomer.

Precursor substances used in the synthesis of PMA are: 4-methoxybenzaldehyde, nitroethane, benzene, methanol and cyclohexane. The reaction yields a viscous red oil. Crystallisation yields lemon-yellow crystals. An alternate synthesis utilises 4-methoxybenzaldehyde, nitroethane and N-amylamine. The intermediate product is 1-(4-methoxyphenyl)-2-nitropropene (melting point 45–46 °C). Substances which have only minor toxicological relevance are used to convert this compound into PMA.

The precursors of both PMA and PMMA are widely available commercially.

PMA can also easily be converted into the amphetamine metabolite 4-hydroxyamphetamine (4-HA) with a melting point of 171–172 °C. Two positional analogues of PMA are known: 2-methoxyamphetamine (2-MA) and 3-methoxyamphetamine (3-MA). Their synthesis is straightforward and similar to that of PMA. 3-MA has been explored in man, but no central effects were noted with a 50 mg dose (2 x 25 mg separated by a three-hour time interval). There do not seem to be any reports of human trials of 2-MA (Shulgin and Shulgin, 1991).

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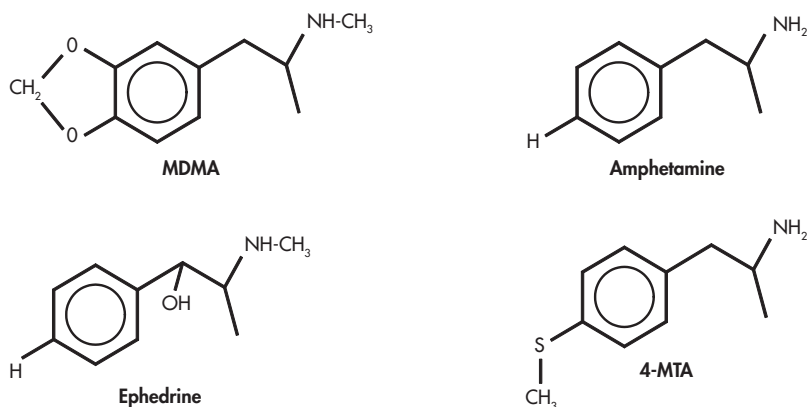
Colour reactions are used to indicate amphetamine derivatives in tablets (Table 3). 2–5 mg of the hydrochloride salt of each drug is used. A given set of colour responses to a combination of field test reagents gives an indication of what may be identified by specific analysis.

Table 3: Colour response of amphetamine derivatives

Reagents	Derivative			
	Amphetamine	MDMA	PMA	PMMA
Marquis	Intense orange-brown	Purple-black	No colour change	No colour change
Mecke	No colour change	Intense green-intense blue	Pale olive green	Pale olive green
Secondary amine	No reaction	Dark blue	No reaction	Blue
Frohde	No colour change	Black	Pale green	Pale green
Mandelin (!)	Blue-green	Black	Rust	Rust
Liebermann	Intense olive green	Intense brown-black	Purple-brown	Purple-brown

(!) Yellow reagent, the interpretation of which is more subjective than for colourless reagents.
Source: Dal Cason, 2001.

Figure 5: Chemical structure of amphetamine and some of its derivatives



The fairly simple molecular structure of the amphetamines (see Figure 5) makes their chemical synthesis and purification relatively easy. Immunoassays of urine are generally used as a first presumptive screening test. GC-MS analysis after extraction and acetylation is one of the most popular techniques for confirming positive initial samples. Unambiguous determination of MS data, however, is often a difficult task because of the spectral similarity of many of the amphetamines, their metabolites and their derivatives (Marson et al., 2000).

The ultraviolet, proton magnetic-resonance, and infrared spectra of PMMA, PMA, and related amphetamine derivatives have been published in papers by Bailey and co-workers (1973; 1975), Clark (1984) and Dal Cason (2000 and 2001). Gas-liquid and thin layer chromatographic systems are presented in detail. The collection of spectra comprises structural isomers as well. This is of interest as the compounds with methoxy groups in positions two or three are less active than other configurations.

It may be of note that other simple phenylethylamines have been detected in powder samples and in urine samples. N-methyl-1-phenylethylamine has been found in quantities of several kilograms in illicit laboratories in the USA and in 'ecstasy' pills in Germany. Thus, chemists analysing pills from the 'ecstasy' scene may find simple phenylethylamines (Marson et al., 2000). 4-methoxyphenyl-2-propanol was identified as a contaminant in some of the tablets seized in the USA (Dal Cason, 2000).

Recently, the presence of other byproducts and impurities from an illicit drug seizure have been described (Coumbaros et al., 1999). Compounds found in PMA preparations in Australia included 4-methoxyphenol, 4-methoxybenzaldehyde, 4-methoxyphenyl-2-propanone, 4-methoxyphenyl-2-propanol, 4-methoxisphenylpropene and, possibly, 4-methyl-5-(4'-methoxyphenyl) pyrimidine. The presence of these compounds suggests that the active drug was prepared from 4-methoxybenzaldehyde via 4-methoxyphenyl-2-propanone using a Leuckardt reductive amination. It was proposed to apply solid-phase microextraction to remove impurities. The possible synthetic routes used by illicit laboratories have been discussed in a recent paper (Kirkbride et al., 2001).

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Legitimate uses of the product

It seems that there is no relevant therapeutic use for PMMA.

The N-methyl substituted 2-MA, which is a positional analog of PMMA, is an adrenergic bronchodilator called methoxyphenamine or orthoxine. It has been used in the prevention of acute asthma attacks in doses up to 200 mg (Shulgin and Shulgin, 1991; van der Schoot, et al., 1962). This compound has been controlled in the UK as a prescription medicine. However, it is no longer available as such on the UK market.

PMMA is thought to strongly and specifically inhibit MAO-A, although this has only been demonstrated for PMA (see later section). Therefore, mood disorders could be a medicinal indication for PMMA. However, because of the toxic effects of PMMA described later, and the availability of a medicinal drug which inhibits MAO-A without causing increased extraneuronal levels of serotonin due to exchange diffusion — a combination which induces toxicity — there is no need to use PMMA for medicinal purposes.

The main metabolite of PMA, 4-hydroxyamphetamine, has been employed therapeutically under the brand name 'Paredrine' in the USA, as a sympathomimetic in patients with heart block or postural hypotension. Effects of cumulative daily doses of 400 mg have been reported, and acute dosages of 80 mg. No central effects related to alertness or mood have been reported (Alles, 1959). A study in man described the intravenous administration of 2 mg, again without reporting any central effects (Severs et al., 1976).

PMMA is a synthetic precursor of the sympathomimetic agent, pholedrine ('Veritol'; Cession-Fossion et al., 1966).

Pharmaceutical form

PMMA

PMMA was originally used as a powder (>100 mg). However, the form in which PMMA is commonly encountered now is as tablets. Tablets containing PMA/PMMA have been seized in Denmark, Germany, Spain, Norway, Austria and Sweden.

They are marked with 'E', 'Mitsubishi' or 'Jumbo' logos.

PMA

PMA was originally used as a powder (50–80 mg). Tablets containing PMA only have been seized in Belgium, Germany, France, the Netherlands, Sweden and the UK.

The tablets seized were marked with 'Superman', 'Elephant', 'Mitsubishi', 'Nike' or 'xTc'.

In contrast to MDMA, MDA, or N-ethyl-3,4-methylenedioxamphetamine (MDE), PMA tablets show no colour change using Marquis reagent (Table 3). This means that PMA tablets can be screened for using a Marquis testing kit.

'DanceSafe', a US-based non-government organisation that is active in the prevention field of drug abuse, reported that PMA does not have the reputation of being a recreational drug. Unlike 'ecstasy', there is no demand for it. It is not being manufactured because people like it: PMA is being manufactured and sold as 'ecstasy' because, unlike MDMA, the chemicals needed to make it are easy to obtain and are not strictly controlled by the government.

Route of administration and dosage

The most common route of administration of PMMA or PMA is oral. Inhalation and intravenous injection of PMA were reported in the mid 1970s.

Toxicology and pharmacology in animals

Preclinical safety data

Single dose toxicity

PMMA: It has been demonstrated that, among various environmental factors influencing the toxicity of amphetamine in mice, aggregation (i.e. the presence of other mice) has the greatest single potentiating influence (Chance, 1946, 1947). This is thought to reflect social stress. *PMMA* did not show any significant difference in acute toxicity in mice under isolated (24 h LD_{50} = 63 mg/kg) or aggregated (24 h LD_{50} = 53 mg/kg) conditions, suggesting a lack of amphetamine-like toxicity (Glennon et al., 1988).

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Table 4: Acute toxicity of PMMA and PMA in animal experiments

	PMMA	PMA
Mouse	LD ₅₀ (1) = 63 and 53 mg/kg	—
Rat	LD ₅₀ (1) = 80–100 mg/kg	6.2 mg/kg; 1 of 2 died within 24 h
Cat	—	LD ₁₀₀ = 25 mg/kg

(1) = 24 h.

— = not available.

Although not fully characterised, the LD₅₀ of PMMA is in the range of 80–100 mg/kg in rats (Table 4). Since this dose is less than twice that required to stimulate locomotor activity (40 and 80 mg/kg), there appears to be a narrow margin between the behaviourally active and the lethal dose of PMMA in rats (Steele et al., 1992).

There are no other published studies of single-dose toxicity.

PMA: 6.2 mg/kg PMA produced abnormal behaviour in two rats (see behavioural studies below). One rat died after one day and a second rat after one week (Smythies et al., 1967).

After producing a rage reaction, PMA was lethal to cats at a dose of 25 mg/kg (Benington et al., 1964; Table 4). The results presented in Table 4 do not allow well-founded conclusions. Nevertheless, they do suggest a higher acute toxicity of PMA than of PMMA. The reason could be that PMMA penetrates the blood-brain barrier less readily than PMA (see pharmacokinetic section). Provided that hyperthermia is the main cause of acute toxicity, a relatively poor penetration of PMMA into the brain would reduce the risk for the induction of acute toxic actions. Hyperthermia is probably caused by activation of 5-HT_{2A} and 5-HT_{2C} receptors in the brain and spinal cord. However, rhabdomyolysis is probably caused by the direct action of PMA or PMMA on skeletal muscle cells. Destruction of myofibres liberates myoglobin which obstructs renal tubuli. The inhibition of MAO-A causes an increase of noradrenaline, serotonin and possibly dopamine in the peripheral organs. Subsequently, hypertension, hypotension, tachycardia, nausea and diarrhoea may occur.

It is interesting to note that para-methoxy-phenylethylamine (PMPEA), which differs from PMA in that it lacks a 1 methyl group in the side chain, did not produce any effect on behaviour. However, when rats were pre-treated with the MAO inhibitor, iproniazid, and 6.2 mg/kg PMPEA, their behaviour was completely disrupted and toxic effects rapidly appeared: the rats lay down and died within a few hours (Smythies et al., 1967). This increase in the toxicity of PMPEA following MAO inhibition has also been reported to produce intense rage reactions and hyperthermia in cats (Benington et al., 1964).

Repeated dose toxicity

Steele et al. (1992) found that, in rats, the lethality caused by PMMA and PMA varied between experiments, ranging from 15 to 43 % for the 80 mg/kg dose. The dose was administered by subcutaneous injection twice daily for four days, and further observation was carried out for one week. The neurotoxic potential of PMMA doses higher than 80 mg/kg was not tested because of the high lethality rate.

Comparison of the neurotoxic potential of PMMA, PMA, and MDMA revealed that the 5-HT-depleting effects of 80 mg/kg PMMA were comparable to those of 80 mg/kg PMA, but were generally less than those produced by 20 mg/kg MDMA. The depleting effects were observed in the hippocampus, frontal cortex and hypothalamus of rat brain. In the striatum, the levels of 5-HT were lower than control levels, but these reductions did not attain statistical significance. The reductions of 5-HIAA (the acidic metabolite of 5-HT) in the striatum were significant for PMA ($p < 0.05$) and MDMA ($p < 0.01$) but not for PMMA. In the hypothalamus, all test compounds caused a similar reduction of 50 % in the concentrations of 5-HT and 5-HIAA.

In addition, Steele and co-workers (1992) performed a dose-response experiment with PMMA. After a dose of 80 mg/kg injected twice daily for four days, they found a reduction of 5-HT ($p < 0.05$) in the hippocampus and frontal cortex but not in the striatum and hypothalamus. The animals were killed one week after the last day of treatment. However, it is interesting to note that the depletion of hypothalamic 5-HT produced by 80 mg/kg PMMA did not achieve statistical significance in one of the two experiments conducted in the same study.

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The neurotoxic action of PMMA appears to be selective for serotonergic systems since striatal dopamine levels were not reduced on a long-term basis by PMMA. In this regard, PMMA closely resembles MDMA and p-chloroamphetamine (PCA). In terms of potency, however, the neurotoxic activity of PMMA is considerably lower than that of MDMA. Structure-activity relationship analysis of neurotoxic amphetamine derivatives revealed that ring substitution at the para position with halogens (PCA) and methoxy groups (PMA and PMMA) yields potent and selective serotonergic neurotoxins. In contrast, the unsubstituted compounds (+)amphetamine and (+)methamphetamine possess dopaminergic neurotoxic activity. N-monomethylation appears to confer serotonergic neurotoxic activity since methamphetamine, but not amphetamine, persistently alters rat brain serotonergic parameters. Notably, N-monomethylation seems to have little influence on the potency or the spectrum of neurotoxic activity of the para-methoxylated compounds: PMA and PMMA are equipotent, as are MDMA and MDA, and PCA and its N-monomethylated analog (Steele et al., 1992).

The number of 5-HT transporters ([³H]paroxetine binding sites) decreased in rat cortex with 80 mg/kg PMMA, suggesting damage or loss of 5-HT terminals ($p < 0.05$; Steele et al., 1992).

The question arises as to whether these findings about neurotoxicity can be extrapolated from animal experiments to humans. Among the structurally-related amphetamine derivatives of PMMA, the neurotoxicity of MDMA is best documented (Ricaurte et al., 2000). Mouse is the one animal species that is relatively resistant to MDMA-induced 5-HT injury. Compared with rodents, primates are more sensitive to the neurotoxic effects of MDMA. The observation that smaller animal species require higher doses of drug to achieve equivalent effects is predicted by the principle of interspecies scaling. This method utilises known relations between body mass and surface area and accounts for differences in drug clearance. Using this method, it is possible to accurately predict the neurotoxic dose of MDMA in rats (20 mg/kg). Specifically, the equivalent dose in monkeys is found to be 5 mg/kg, a dose that has in fact been shown to be neurotoxic in monkeys. Based on the dosages that are neurotoxic for rats or monkeys, it is possible to predict the dosage of MDMA that would be neurotoxic in humans. Taking the neurotoxic dose of 5 mg/kg in a 1 kg squirrel monkey, the equivalent dose in humans is found to be 1.28 mg/kg; or approximately 96 mg in a 75 kg individual. Please note that this is a model calculation carried out according to Ricaurte and colleagues' methods and does not necessarily represent the real toxicity.

Extrapolating from the report of Steel et al. (1992) that a dose of 80 mg/kg PMMA causes a reduction of 5-HT in some of the brain regions of rats, the analogue calculation indicates that 384 mg PMMA would be toxic in humans. It should be noted further that the dose of 80 mg/kg is the approximate dose at which 50 % of rats die.

With respect to PMA, Shulgin (1978) speculated that PMA has a therapeutic index of about 2.5 and that as little as 150 mg may prove to be a toxic dose in humans.

Reproductive function

There are no reports about the action of PMMA or PMA on reproductive function, embryo-foetal or perinatal toxicity, nor about their mutagenic and carcinogenic potential.

Pharmacodynamics

In vitro tests

Actions on neurones: There is no information regarding the *in vitro* activity or metabolism of PMMA. Results on PMA are probably representative for PMMA.

In mouse brain, homogenate with a K_i value of 0.22 μM , PMA is over 20 times as potent as (+)amphetamine (6 μM , o-methoxyamphetamine 9 μM , m-methoxyamphetamine 23 μM) as an inhibitor of 5-HT oxidation by MAO. PMA is highly selective towards A-type MAO and possesses only weak activity against B-type enzyme (Green and Hait, 1980). The high inhibitory potency of PMA has been confirmed using crude mitochondrial suspension from rat brain ($\text{IC}_{50}=0.3 \mu\text{M}$). By comparison, the inhibition constants (K_i) of the specific MAO-A inhibitor, clorgyline, is 0.054 μM (competitive initial non-covalent interaction) and of moclobemide is 200 μM (Cesura and Pletscher, 1992). Others reported a K_i -value of 0.0063 μM for clorgyline using crude mitochondrial fraction from rat brain as the source of MAO-A (May et al., 1991).

The high inhibitory potency of PMA is an important observation with respect to the toxic actions of PMA and probably of PMMA. As mentioned before, phenylpropylamines such as PMA and PMMA are much more toxic than phenylethylamines. This is explained by the fact that the former compounds are poor substrates for MAO.

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Therefore, the inactivation of phenylpropylamines by oxidative transamination of the side chain is much slower than that of the phenylethylamines. Studies with positional analogues demonstrate that the inhibitory potency is highest in para-substituted amphetamines such as PMMA and PMA, and that the difference in potency is more than 40-fold compared with the ortho- and meta-substituted compounds.

Another series of experiments should be mentioned which might contribute to the understanding of the *in vivo* actions of PMMA. These are related to the effects of PMMA on dopaminergic and serotonergic neurones. While there are no relevant studies for PMMA or PMA, there are findings with MDMA, which is structurally similar to PMMA. MDMA has a strong binding affinity for the 5-HT (serotonin) transporter (SERT), and inhibits 5-HT reuptake into hippocampal synaptosomes ($EC_{50}=0.35\pm 0.03\ \mu\text{M}$) more potently than dopamine uptake into striatal synaptosomes ($EC_{50}=1.14\pm 0.03\ \mu\text{M}$; Crespi et al., 1997). On the other hand, amphetamine binds with a high affinity to the dopamine transporter (DAT) and inhibits dopamine reuptake into striatal synaptosomes ($EC_{50}=0.13\pm 0.04\ \mu\text{M}$) more potently than 5-HT reuptake into hippocampal synaptosomes ($EC_{50}=4.51\pm 0.64\ \mu\text{M}$). Lastly, fenfluramine binds with a high affinity to SERT and is a much more potent inhibitor of 5-HT reuptake ($EC_{50}=0.90\pm 0.40\ \mu\text{M}$) than of dopamine reuptake ($EC_{50}=11.2\pm 0.13$). Fenfluramine is mentioned because it is a model substance for the activation of serotonergic neurones with numerous reports on the *in vivo* effects. It is important to note, however, that although MDMA has a higher affinity for SERT, there is a greater total efflux of extracellular dopamine over that seen for 5-HT at behaviourally active doses (White et al., 1996).

Metabolism: Phenylisopropylamines interact with CYP 2D6 as substrates and/or as inhibitors. The apparent K_i values of PMA (24 μM), (+)methamphetamine (25 μM) and (+)amphetamine (26.5 μM) were similar (Wu et al., 1997). PMMA was not investigated. From findings with amphetamine and methamphetamine, it can be concluded that N-methylation does not affect the affinity of phenylisopropylamines to the cytochrome isoenzyme. Therefore, PMMA probably has the same affinity to CYP 2D6 as PMA (~24 μM).

The use of PMMA may cause metabolic interactions with other drugs that are CYP 2D6 substrates and the potential for polymorphic oxidation via CYP 2D6 may be a source of interindividual variation in its toxicity. Interacting medical drugs would be fluoxetine, tricyclic antidepressants, β -adrenoceptor blockers, and methoxymorphinans.

Deficiency in the 4-hydroxylation of amphetamine and the O-demethylation of PMA (and probably PMMA) were two early observations that led to the discovery of the CYP 2D6 polymorphism (Kitchen et al., 1979).

In vivo tests

Effects on central nervous system: Rats given the highest doses of PMMA (40 and 80 mg/kg) exhibited clear signs of sympathomimetic stimulation; including salivation, piloerection, lacrimation, and sometimes convulsions (Steele et al., 1992). It is not clear whether the neuronal basis of this is sympathomimetic activation as assumed by the authors. Most of the symptoms can be induced by serotonergic stimulation as well. However, the inhibition of MAO-A produces an increase of noradrenaline in the brain (Hegadoren et al., 1995). Thus, both types of neurones presumably contribute to the *in vivo* effects of PMMA.

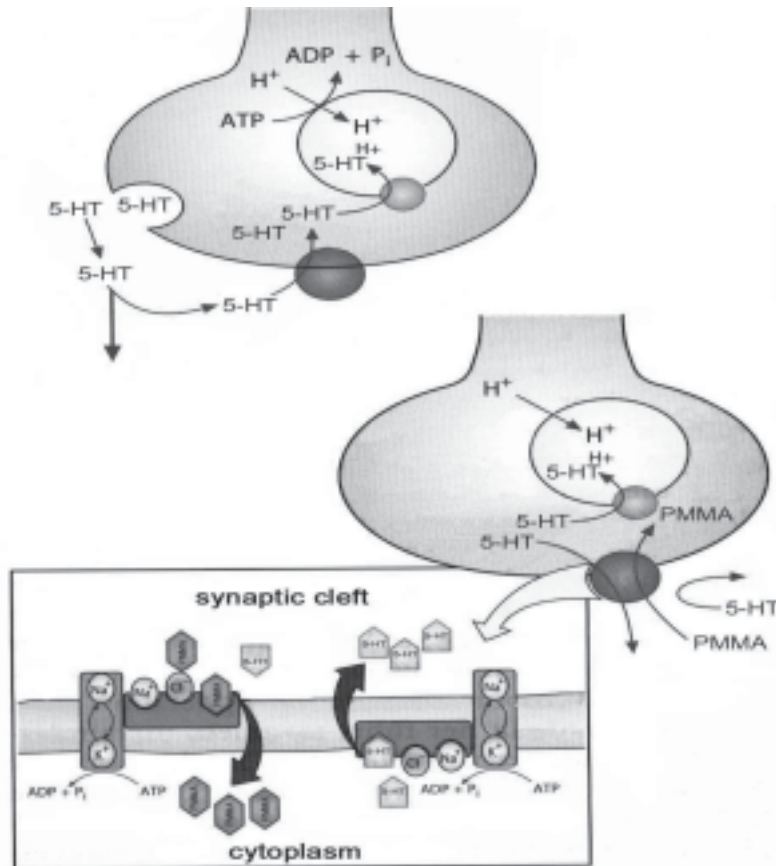
PMMA produced an unusual cataleptic effect in cats and rats when administered by the intracisternal or intraventricular route. This effect, though less marked, was also observed in mice given PMMA (Michaux, 1967; Michaux et al., 1965).

PMMA did not produce significant locomotor stimulation at doses up to 30 mg/kg in mice. At doses greater than its LD₅₀ dose, PMMA produced behavioural effects such as hyperactivity and vocalisation, which were similar to those observed with amphetamine. In this respect, PMMA was weaker than PMA which, in turn, was weaker than racemic amphetamine and racemic methamphetamine (Glennon et al., 1988). It can be concluded from both reports that PMMA is a very weak central stimulant and less active than PMA. Amphetamine is at least six times more potent a central stimulant than PMMA.

The neuronal basis for the hyperactivity and sympathomimetic stimulation is not clear. The inhibition of MAO-A could contribute to the central and peripheral effects observed in animals and in some, but not all, human volunteers after the intake of PMMA. High doses of serotonergic compounds, such as fenfluramine, induce a so-called 'serotonin syndrome' with hyperactivity, hyper-reactivity, hind limb abduction, lateral head weaving, reciprocal forepaw treading, rigidity, Straub tail, tremor and piloerection in animals. Even higher doses cause convulsions, coma and death. It is important to note that many of these effects were observed only when rodents had been pre-treated with MAO inhibitor (e.g. iproniazid).

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Figure 6: Molecular action of PMMA on the serotonergic presynapse. PMMA is taken up into the synapse in exchange for cytoplasmic 5-HT



Source: Modified from Rommelspacher (2001).

It is important to note that the carrier-mediated release of 5-HT is calcium and action-potential independent (Figure 6). The effect is greatly increased by the concomitant application of transmitter precursors (e.g. 5-hydroxytryptophan) or inhibitors of metabolising enzymes (e.g. MAO inhibitors). The extent to which both mechanisms contribute to the behavioural effects of PMMA is not clear. 4-MTA, which has similar effects and is presumably equipotent for the inhibition of MAO-A, induced a maximal increase of 5-HT in the dorsal hippocampus of rats of about 2000 % compared with baseline

40 minutes after a 5 mg/kg injection. The levels declined slowly thereafter, which was thought to be due to the MAO-A inhibitory properties of 4-MTA (Scorza et al., 1999). From studies with MDMA, it is known that low doses (3 mg/kg of the more potent, positive, MDMA enantiomer) elicit hypermotility in rodents by activating 5-HT_{1B/1C} receptors. This effect is inhibited by specific receptor blockers and is not seen in 5-HT_{1B} knock-out mice. Higher doses induce hypermotility involving the 5-HT_{2A} and dopamine receptors (Bankson and Cunningham, 2001).

The actions of PMMA and PMA observed in animals and humans strongly suggest a dominant role for 5-HT neurones. This notion is supported by behavioural experiments delineating the effects of specific 5-HT receptor agonists and antagonists, and the effects of PMMA and PMA in knock-out mouse models. The activation of 5-HT_{1B} receptors, which probably mediate the actions of low doses of PMMA, causes hypophagia, hypothermia, penile erection, increased release of corticosterone and prolactin. 5-HT_{1B} receptor agonists have an anti-aggressive action and induce myoclonic jerks. The activation of 5-HT_{2A} receptors, which probably mediate the action of medium and high doses of PMMA, causes motor activity, hyperthermia, head twitches (in mice), wet dog shakes (in rats), discriminate DOM (a hallucinogen, from 5-HT₁-R agonists) hallucinations, and elevation of cortisol, ACTH, renin, and prolactin. The activation of 5-HT_{2C} receptors, which probably also mediate the actions of medium and high doses of PMMA, causes hypolocomotion, hypophagia, anxiety, hyperthermia, penile erection, tonic inhibition of dopaminergic mesolimbic/mesocortical neurones, inhibition of noradrenaline release, and hallucinations.

When evaluating the *in vitro* and *in vivo* actions of PMMA, pharmacokinetic aspects should always be considered (see section below). PMA is a weak central stimulant ($ED_{50}=9.5 \mu\text{mol/kg}$) compared with amphetamine ($ED_{50}=1.8 \mu\text{mol/kg}$) and methamphetamine ($ED_{50}=1.5 \mu\text{mol/kg}$) (Young and Glennon, 1986).

In comparative studies, 5.28 mg/kg PMA caused no change in striatal levels of dopamine whereas metabolites were lowered, suggesting inhibition of MAO (Hegadoren et al., 1995). Levels of noradrenaline were elevated in the hippocampus, striatum, and cortex. Equimolar doses of amphetamine, MDMA, MDA, and MDE were inactive, supporting the idea that PMA, and probably PMMA, have a different molecular action. The levels of 5-HT were slightly elevated whereas those of the metabolite 5-HIAA were lowered (Hegadoren et al., 1995).

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This finding is again consistent with a strong inhibition of MAO-A by PMA. The high intrinsic potency of PMA against 5-HT oxidation by MAO-A was demonstrated in mice under *in vivo* conditions (Green and ait., 1980). The authors estimated that 0.5 mg/kg PMA inhibited 50 % of enzyme activity. This dose is only about one quarter of the equipotent dose of the irreversible MAO-A inhibitor, phenelzine. Whereas inhibition by phenelzine persists for several days, the high level of inhibition by PMA is maintained only for a short time, and the extent of inhibition declines rapidly after one hour.

A recent report compared the *in vivo* effects of PMA and MDMA on serotonergic and dopaminergic neurones (Daws et al., 2000). *In vivo* chronoamperometry was used to measure the effects of PMA and MDMA in anaesthetised rats. MDMA induced the release of dopamine and inhibited uptake of both dopamine and 5-HT. In contrast, PMA was a relatively weak releasing agent and did not inhibit dopamine uptake. However, PMA potently inhibited uptake of 5-HT. It can be concluded from these findings that the acute effects of PMA (and probably PMMA) are more likely to be associated with alterations in serotonergic rather than dopaminergic neurotransmission.

Effects on the cardiovascular system: PMMA produces cardiovascular and other sympathomimetic effects by what is believed to be an indirect mechanism (Cession-Fossion et al., 1966). A 0.2 mg/kg dose showed prolonged cardiovascular effects in the dog (Cheng et al., 1974).

The cardiovascular effects of PMA have been investigated in conscious rats, by radiotelemetry. The effects of PMA were compared with those of MDMA. The influence of ambient temperature on these responses was also investigated (Irvine et al., 2001). In contrast to MDMA, which releases both dopamine and 5-HT, PMA appeared to be more selective in releasing only 5-HT, not dopamine or noradrenaline. This may account for their markedly different cardiovascular profiles. PMA (10, 15, and 20 mg/kg) lowered, rather than increased, heart rate. The bradycardia produced by PMA was of considerable magnitude and was sustained at 20 °C ambient temperature but not at 30 °C. MDMA produced a minor increase in heart rate, which was only evident at the lowest dose. Furthermore, bradycardia after PMA administration was not a result of increased BP. PMA and MDMA (10 and 20 mg/kg) decreased both systolic and diastolic BP. This effect was sustained for PMA, whereas in MDMA-treated animals the BP returned to normal at about 45 minutes. At 30 °C, systolic and diastolic BPs were significantly increased for both drugs at 10 and 20 mg/kg.

The effects of PMMA and PMA on respiratory, gastrointestinal, and genito-urinary systems, as well as on liver and kidneys, have not been investigated.

Behavioural studies: In order to determine the physiological nature of a given compound (entactogenic, hallucinogenic, soporific, etc.) without exposing human subjects to unknown consequences, drug discrimination studies are often used. Briefly, drug discrimination studies are conducted by training test animals to differentiate the effect(s) of a 'training' drug from those of a saline (control, vehicle) solution. When the test animal can reliably differentiate or discriminate the training drug from a saline solution, they may then determine if the effects of a new compound mirror the effects of the training drug. If the animals' response to the new drug correlates with their response to the training drug, the tested compound is said to 'generalise' (resemble) the training drug (Dal Cason, 2001).

Unexpectedly, PMMA has previously been shown to lack amphetamine-like or hallucinogen-like stimulus properties in animals in drug discrimination studies. For example, in tests of stimulus generalisation, neither a (+)amphetamine stimulus nor a DOM stimulus generalised to PMMA. Similarly, it has been shown that stimulus generalisations do not occur in animals trained to discriminate MDMA from vehicle. In order to further characterise this unique agent, six rats were trained to discriminate 1.25 mg/kg of PMMA ($ED_{50}=0.44$ mg/kg) from saline vehicle. The PMMA stimulus failed to generalise to (+)amphetamine or the hallucinogen DOM. Stimulus generalisation occurred to (\pm) MDMA ($ED_{50}=1.32$ mg/kg) and S(+)-MDMA ($ED_{50}=0.48$ mg/kg). Partial generalisation occurred with R(-)-MDMA, PMA, 3,4-DMA and fenfluramine. The PMMA stimulus also generalised to the α -ethyl homologue of PMMA ($ED_{50}=1.29$ mg/kg). Taken together, these findings suggest that PMMA is an MDMA-like agent that lacks the amphetamine-like stimulant character of MDMA (Glennon et al., 1997).

Researchers have investigated whether the stimulant effects in drug discrimination experiments are stereoselective (Young et al., 1999). S(+)-PMMA ($ED_{50}=0.32$ mg/kg) was found to be at least as potent as racemic PMMA ($ED_{50}=0.41$ mg/kg), whereas R(-)-PMMA failed to result in complete stimulus generalisation. The results support the concept that PMMA and MDMA share considerable similarity with respect to their stimulant properties in animals except that PMMA lacks the amphetaminergic

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stimulant component of action associated with MDMA. These findings suggest that the S(+)-enantiomer of PMMA is the active compound.

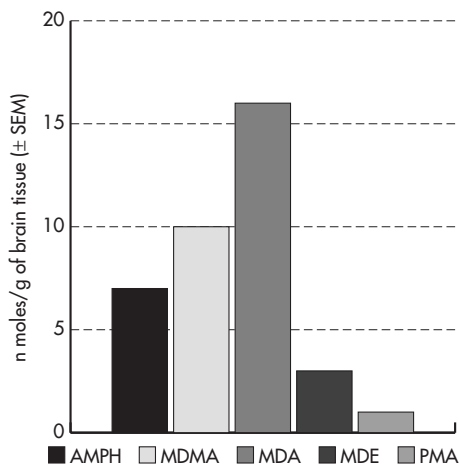
Based on the Sidman avoidance schedule and the Bovet-Gatti profiles, Smythies and colleagues have developed an animal test which predicts the hallucinogenic effect of a drug on man (1967). The authors reported that PMA proved the most potent hallucinogen they have so far tested (with the exception of LSD). This statement is based on findings in only two rats. At a dose of 3.1 mg/kg, it produced a typical 'low dose hallucinogenic' Bovet-Gatti profile quite distinct from amphetamine. Doses of 6.2 mg/kg PMA induced bizarre behaviour in both rats tested. Although the rat could walk about normally, and appeared to be able to eat and drink normally, it frequently walked backwards — a typical mescaline effect. It would show exaggerated startled responses in the absence of external stimuli and would frequently engage in strange behaviour reminiscent of shadow boxing — rearing and pawing in the air. If placed on a table, it would walk, apparently normally, towards the edge and fall off, and would do this repeatedly if replaced on the table. This period of abnormal behaviour lasted until the rat died (after one day and one week, respectively; Smythies et al., 1967). This report had a strong impact on the drugs 'scene' in the 1970s. It contributed greatly to the abuse of PMA.

With respect to the locomotor stimulating effect of PMA in rats, a comparative study investigated equimolar effects of five amphetamines (32 µmol/kg). PMA did not differ from vehicle (Hegadoren et al., 1995). MDMA (10 and 20 µg/kg) increased locomotor activity in rats in contrast to PMA (10 µg/kg) which was without effect (Irvine et al., 2001).

Pharmacokinetics in animals

There are no published reports on the pharmacokinetics of PMMA in animals. There is one report that compares equimolar doses of five amphetamines in rats 3h post-injection. The level of PMA in the brain was about six times lower than that of amphetamine and 10 times lower than that of MDMA (Figure 7; Hegadoren et al., 1995). These findings suggest a poor penetration of PMA into the brain. Because MDA levels were approximately 50 % higher than those of MDMA, PMMA might penetrate the blood-brain barrier to a lesser extent.

Figure 7: Drug levels in whole brain 3h post-injection of equimolar doses (32 $\mu\text{mol/kg}$) of five drugs



Source: Hegadoren et al., 1995.

Becket and Midha (1974) have examined the metabolism of PMA by liver preparations of rabbit, guinea pig, and rat. Four side-chain oxidation products, the N-hydroxy derivative, oxime, phenyl-2-propanone, and phenyl-2-propanol were characterised. Further findings are reported under *in vitro* studies (see above).

O-demethylation is the major metabolic reaction of the drug in the rat, dog, and monkey.

Human pharmacology

Laboratory studies in volunteers

Effects on cognition and behaviour

PMMA: There is a report of *PMMA* use by Shulgin (Shulgin and Shulgin 1991) in which he took 110 mg *PMMA*. He states:

I was compulsively yawning. There was some eye muscle disturbance, a little like the physical side of MDMA, but there was none of its central effects. But all the hints of the cardiovascular (effects) are there. By the fourth hour, I am pretty much back to baseline, but the yawning is still very much part of it. I might repeat this, at the same level, but with continuous close monitoring of the body.' Later he wrote *I tried it and I didn't like it.*

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Shulgin commented in the same report:

N-methylhomologues of primary amines maintain the stimulant component, but the 'psychedelic' contribution is generally much reduced. And as PMA is a pretty pushy stimulant with little if any sensory sparkle, why bother with the N-methyl compound?

The report by Shulgin of no stimulatory activity with PMMA, in contrast to a weak stimulatory action with PMA, agrees well with observations in animals. There might be pharmacokinetic reasons for the lack of central effects with this specific dose of PMMA. Although there are no specific investigations, the distinct cardiovascular effects which are caused by peripheral activation of 5-HT mechanisms (Irvine et al., 2001) support this notion. Further human experiences with PMMA are reported below.

PMA: PMA was ingested by five normal subjects in a dose range of 10–65 mg (PMA HCl). No psychotic or other behavioural changes were reported (Schweitzer et al., 1971). However,

With 60 mg, I found the effects reminiscent of DET (N,N-diethyltryptamine), distinct after-images, and some paraesthesia. I was without any residue after 5 hours.

Shulgin (1978) observed,

With 70 mg it hit quite suddenly. I had a feeling of druggedness, almost an alcohol-like intoxication, and I never was high in the psychedelic sense.

He also reported that,

A major metabolite of amphetamine is 4-hydroxyamphetamine. It has been long known that with chronic amphetamine usage there is the generation of tolerance. When the daily load gets up around one or two hundred milligrams, the subject can become quite psychotic. The question was asked: might the chronic amphetamine user be methylating his endogenously produced 4-hydroxy-amphetamine to produce PMA, and maybe this is the agent that promotes the psychosis? To address this question, several studies were done with normal subjects, about 20 years ago, to see if 4-MA might produce a psychotic state. It produced excitation and other central effects, it produced adrenergic pressure

effects, and it consistently produced measurable quantities of 4-MA in the urine, but it produced no amphetamine-like crazies (dose range 10–75 mg PMA). And since the administration of up to 629 mg of amphetamine over a period of 51 h (5–10 mg/h) produced no detectable PMA in the urine, this theory of psychotomimesis is not valid (Angrist et al., 1969) (Shulgin, 1978).

From these studies, Shulgin (1978) concluded that PMA is a treacherous drug to study in human subjects. The compound has an unusually steep dose-response curve in man. At dosages of 40 mg or less, it is without either peripheral or central effects. Yet at dosages of 60–80 mg, the effective dose for induction of a psychotomimetic syndrome (Shulgin et al., 1969), there have been incidents of precipitous hypertension and cardiovascular stimulation (Angrist, personal communication). The psychotomimetic state occurs quite suddenly about an hour after ingestion of the drug, and a plateau of central intoxication occurs within the second hour (Shulgin, 1978).

The report of Shulgin et al. (1969) has been quoted in connection with the psychotomimetic effect of PMA. Mescaline was selected as the initial compound for this study. Although it is less active than most psychotomimetics, it has a close structural relationship to compounds known to be naturally present in humans. No psychotic symptoms were observed in this study. In contrast to what was reported by Smythies and co-workers for rats (1967), PMA was a weak psychotomimetic in humans (5 mescaline units compared with LSD's 4 600 mescaline units in humans). The three-carbon side chain seems to provide optimal activity. This is presumably because such molecules are poor substrates for MAO, the enzyme which deaminates alpha-unsubstituted phenethylamine.

Cardiovascular effects

PMMA: One hour after taking 110 mg PMMA orally, Shulgin (Shulgin and Shulgin, 1991) reported that his pulse was over 100 beats/minute. All indications of the cardiovascular effects of MDMA were there.

PMMA: The somatic effects can persist for over two hours, together with BP elevation. Paraesthesia can still be observed four hours after administration (Shulgin, 1978).

With 60 mg at just over an hour, there was a sudden blood pressure rise, with the systolic going up 55 mm. This was maintained for another hour (Shulgin, 1978).

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The delay in the cardiovascular effects cannot be explained. As already discussed, the cardiovascular effects of medium doses of PMA are caused by activation of peripheral serotonergic mechanisms.

Effects of overdose

Blood concentrations of PMA greater than 0.5 mg/l seemed likely to be associated with toxic effects. Post mortem PMA concentrations were 0.24 to 4.9 mg/l (mean 2.3 mg/l) for femoral blood and 1.4 to 21 mg/kg (mean 8.9 mg/kg) for liver.

Pharmacokinetics in humans

There are no pharmacokinetic reports of human use of PMMA in the literature. From studies on PMA, it can be concluded that demethylation of the 4-methoxygroup is the major metabolic inactivation step. Oxidation of the side chain probably occurs slowly because MAO-A, the enzyme involved, oxidises phenylpropylamines much more slowly than phenylethylamines, despite the high affinity of PMA (and probably PMMA) for the enzyme.

PMMA is demethylated in the liver by the cytochrome P₄₅₀ 2D6 isoenzyme (see *in vitro* studies and PMA for details). Repeated intake of PMMA might cause inhibition of the isoenzyme due to a so-called mechanism-based inhibition (see below for details).

Three adult male volunteers of known oxidation phenotype (2 extensive oxidisers, 1 poor oxidiser) each took a single oral dose of 5 mg of 4-methoxy [¹⁴C] amphetamine (a form of PMA). Urine was collected over 24 hours. 82.6, 76.8, and 49.0 % of the ingested radioactivity was detected in the urine of each of the volunteers, respectively. PMA is metabolised by O-demethylation and by side-chain oxidation. Marked intersubject variations were observed. The 2 extensive oxidisers excreted mainly 4-hydroxyamphetamine (63 and 49 %, respectively) together with smaller amounts of 1-(4'-methoxyphenyl) propan 2-one oxime (4.5 and 5.5 %, respectively) and 4-hydroxynorephedrine (6.1 and 4.6 %). The poor oxidiser excreted unchanged PMA (28 %) together with products of side chain oxidation, namely 1-(4'methoxyphenyl) propan-2-one oxime (9.9 %), 1-(4'-methoxyphenyl)propan-2-one (1 %) and 4-methoxybenzoic acid (0-2 %). About 9 % of caucasians are characterised by this oxidation defect, which is genetically determined and inherited as a recessive trait. The authors speculated that individuals who carry the defective oxidative trait could

be poor demethylators and therefore de-activators of O-methylated psychotoxins (Kitchen et al., 1979).

Phenylisopropylamines interact with the cytochrome isoenzyme CYP 2D6 as substrates and/or inhibitors. The apparent K_i -values of PMA (24 μM), (+)methamphetamine (25 μM) and (+)amphetamine (26.5 μM) were equal. PMMA was not investigated (Wu et al., 1997).

Repeated intakes of PMMA and PMA might cause inhibition of the isoenzyme due to a so-called mechanism-based inactivation. This has been demonstrated in rats with a model compound, allyloxymethamphetamine. The aromatic ring oxidation seems to be a prerequisite for the inhibition (Lin et al., 1996). Both PMA and PMMA fulfil this criterion. The relevance of the inactive CYP 2D6 isoenzyme for the reduced metabolism of amphetamines has been demonstrated *in vivo* in the Dark Agouti model. Female rats metabolise substrates of the isoenzyme more slowly (Colado et al., 1995). The hyperthermic response following MDMA was enhanced, and the plasma concentrations were 57 % higher than in controls. The hyperthermic response was higher in rats pre-treated with a substance which competes selectively for the isoenzyme (quinine) suggesting that other substrates of the isoenzyme reduce the inactivation of the amphetamines if combined (see below).

Excretion

In man, PMA is extensively metabolised, since the average excretion of PMA was 6.7 % of the administered dose with a range of 0.3 to 15 % (Schweitzer et al., 1971).

After oral ingestion of PMA, about 80 % of the dose is excreted in the urine within 24 hours with more than 15 % unchanged, 18 to 25 % free 4-hydroxyamphetamine and 50 % conjugated (containing 21 % 4-hydroxy-amphetamine and 7 % N-hydroxy-PMA), and 5 % 4-hydroxynorephedrine (EMCDDA, 2001a).

No calculation of the elimination half-life of PMMA and PMA has been reported.

Pharmacokinetic interactions

The use of PMMA and PMA may cause metabolic interactions with other drugs that are CYP 2D6 substrates and the potential for polymorphic oxidation via CYP 2D6

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may be a source of interindividual variation in their abuse liability and toxicity. Interacting medical drugs would be: inhibitors of the neuronal transport mechanism of serotonin (e.g. fluoxetine), tricyclic antidepressants (e.g. imipramine), b-adrenoceptor blockers (e.g. metoprolol), deprenyl (N-propargyl methamphetamine), inhibitors of MAO-B; and methoxymorphinans.

The interaction with fluoxetine might be of special importance because some MDMA users take fluoxetine to prevent neurotoxic damage. Fluoxetine has been detected in the urine samples of some PMA/PMMA users.

Clinical experience

Studies of street users (Table 5)

In the early 1970s, the illicit use of PMA was first identified in the USA and Canada.

Table 5: Fatalities from PMA and PMMA/PMA

Year	Number of victims	Country	Remarks	Reference
1973	Nine	Canada	PMA; low ethanol (4); traces MDA (1). PMA concentration in blood considerably lower than that in fatal MDA poisoning	Cimbura, 1974
1973	Unknown	USA — Kansas City; Atlanta		Bailey, K., Legault, D., Verner, D., Microgram VI, 1973
1995	Ten	Australia — South Australia; Queensland; Western Australia	PMA; other amphetamines (9)	Felgate et al., 1998; Byard et al., 1998
1993	One	Spain	PMMA; MDEA; MDM; ethanol	Lora-Tamayo et al., 1997

Year	Number of victims	Country	Remarks	Reference
1995	One	Spain	PMA; p-OH-AMP	Lora-Tamayo et al. 1997
2000	Ten	USA — Illinois: 3; Florida: 7	PMA and other illicit drugs	American newspapers
2000	One	Austria	PMA; PMMA	EMCDDA, October 2001
2000	Three	Denmark	PMA, PMMA (2); PMA, PMMA, MDMA (1)	EMCDDA, February 2001
2000	Two	Germany	PMA	Europol, July 2000
2001	Four	Belgium	PMA, MDA, Amph (1); PMA, MDMA, MDA, Amph (1); PMA, traces norephedrine (1); PMA, MDMA (1)	EMCDDA, October 2001

Canada

Between March and August 1973, there were nine deaths of young people in Ontario that were attributed to PMA (Cimbura, 1974).

PMA was the only chemical toxin found in significant amounts. Low levels of alcohol were present in four cases and, in one case, traces of MDA were found in the bile and urine but none were detected in the blood.

These deaths indicate that PMA is more toxic than MDA. This is supported by the fact that the range of PMA concentrations found in the blood of the victims was considerably lower than that of MDA.

USA

With respect to fatalities in the USA in the early 1970s, Shulgin et al. (1991) reported that PMA became widely distributed in the USA as the sulphate salt and in Canada as the hydrochloride. This usage was perhaps inspired by some studies in rats which reported that PMA was second only to LSD in potency as a hallucinogen (Smythies et al., 1967). Several deaths occurred, probably following overdose. It was clear that PMA was involved as it was isolated from both urine and tissue during post mortem.

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Comments collected in association with 10 deaths implied that the quantities ingested were of the order of hundreds of milligrams.

The causes of the deaths are not clear. Common symptoms were hyperthermia (~42 °C), possibly dehydration, and cardiac problems (e.g. BP 180/130 mmHg, pulse 140 beats/min). It is noteworthy that chronic dosing of MDMA produced sensitisation to both hyperthermic and hyperkinetic responses in rats. Furthermore, high ambient temperature and water deprivation augmented the hyperthermia (Dafters, 1995). These findings suggest that individuals who regularly use 'ecstasy' have a higher risk of developing hyperthermia. Whether there is a cross-sensitivity with PMMA is not known.

Other reasons might be metabolic defects and mechanism-based inactivation of CYP 2D6 isoenzyme, which might cause delayed inactivation of PMMA.

Australia

PMA has only been available in Australia since late 1994. Between June 1996 and January 1997, there was a sudden increase in the number of patients in Adelaide suffering from amphetamine toxicity. Among a total of 16 admissions, 14 patients were found to have PMA in their urine.

Since 1995, 10 PMA deaths have been reported in Australia. Behaviours that were observed before death were 'thrashing around', extreme agitation, convulsions, jaw rigidity and sweating. Features of rhabdomyolysis and renal failure were found at autopsy, including disseminated intravascular coagulation and hyperkalaemia in several cases. The authors (Felgate et al., 1998; Byard et al., 1998) commented that MDMA was of significance in two of the cases and amphetamine and methamphetamine in one case each; the significant factor in each case was the toxic effects of PMA. PMA would appear to be more toxic than other common amphetamine derivatives. All the PMA-related deaths involved oral administration.

The PMA levels were considerably lower in the Canadian deaths (Cimbura, 1974), being in the range of 0.3–1.9 mg/l for the blood samples.

Spain

A paper was published that compiled the toxicology data from all the fatalities investigated from 1993 to 1995 by the Instituto Nacional de Toxicologia in Madrid, in which at least one amphetamine derivative was found in the blood (Lora-Tamayo et al., 1997). In 1995, one case had high PMA levels in the blood (5.7 mg/l). Other amphetamines detected were p-OHAMP and a metabolite of PMA (0.35 mg/l); no other amphetamines, MDMA, MDEA, or MDA were found. A second case found PMMA (1.15 mg/l) and 2.00 mg/l MDEA, 0.3 mg/ml MDM and ethanol (0.2 g/l) in the blood. The authors commented that, 'the meaningful interpretation of the contribution of the amphetamine derivative to the death in those cases is problematic.'

Austria

The Austrian Reitox national focal point reported on the death of a 17-year-old man in July 2000. Forensic analysis confirmed that PMA and PMMA were involved in this death. The concentrations found in the blood were 1 mg PMA/l and 0.4 mg PMMA/l.

Denmark

The Danish Reitox national focal point notified three deaths associated with PMA/PMMA which occurred between July and September 2000. It was concluded from forensic analysis that two deaths at the beginning of July were caused by PMA and PMMA poisoning. In the first case, the poisoning was caused by PMA and PMMA as well as MDMA, whereas the second and third case were caused by poisoning with PMA and PMMA alone.

Germany

Europol reported that PMA was implicated in two deaths in 2000.

Belgium

The Belgian Reitox national focal point reported on the following fatal cases: the first death in which PMA was involved occurred in February 2001. Forensic analysis of a blood sample revealed MDA (0.39 mg/ml), amphetamine (0.22 mg/ml) and PMA (1.43 mg/ml). The report concluded that the subject died due to the effects of a cocktail of several amphetamines.

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According to his friends, a young man from the region of Leuven used 'ecstasy' regularly and had ingested seven tablets on the evening of his death (July, 2001). The analysis of the blood revealed MDMA, MDA, amphetamine and PMA. Traces of cannabis, codeine (possibly due to medical treatment with Dafalgan codeine), and alcohol were detected as well.

Two deaths were reported from the region of Antwerp in July 2001. Analysis of the blood samples yielded PMA (1.7 mg/ml blood) and traces of norephedrine in the first case, and PMA (3.4 mg/ml blood), and MDMA (0.4 mg/ml blood) in the second case.

Potential for dependence in humans

- Users are misled by the logo which suggests to them that the tablet contains MDMA.
- Reports of drug-experienced users of PMMA and the findings from animal studies suggest a low risk for PMMA dependence. The users of PMMA reported mental stimulation after the intake of high doses (e.g. 215 mg PMMA). Other pleasant effects encountered with MDMA were not reported (i.e. euphoria, a general sense of well-being, emotional warmth, and closeness and empathy for others). In contrast to the effects of MDMA, the users reported reduced motivation to talk and to get involved with others. They suffered from unwanted physical effects such as transpiration, severe nystagmus, body stiffness, and pain in the stomach and head. They did not feel out of control.
- The results of animal experiments suggest that PMMA does not activate mesolimbic/mesocortical dopaminergic neurones, a prerequisite for the induction of drug seeking behaviour in animals. There is evidence for a reduction of the activity of dopaminergic neurones *in vivo* (catalepsy in cats and rats).

Clinical safety

Based on experience with MDMA, a major concern with PMA and PMMA is the neurotoxic potential. An interesting hypothesis for the possible mechanisms of MDMA neurotoxicity is the formation of thioether adducts. One of the hydroxyl groups of dihydroxymethamphetamine, the main metabolite of MDMA, reacts with the SH group of either glutathione or cysteine. The main metabolite of PMA is 4-hydroxyamphetamine. Demethylation of the 4-methoxygroup is probably the major inactivation step for PMMA metabolism as well. When such amphetamine adducts are administered to the

striatum or cortex, they are able to reduce serotonin concentrations, to produce long-term depletion (seven days), and to induce neurodegeneration of serotonergic neurones similar to that observed after systemic MDMA administration (Bai et al., 1999; Miller et al., 1996 and 1997).

Most of the psychotropic actions of MDMA, such as euphoria, emotional warmth, empathy for others, mental stimulation and a general sense of well-being are not reported with PMA and PMMA. The user expecting these effects probably assumes that the dose is too low and takes more tablets. The therapeutic index of PMMA and PMA is much lower than that of MDMA and reaches toxic doses almost within the range at which psychotropic effects occur. PMMA is less effective than PMA. Animal experiments suggest that PMMA is less toxic than PMA (see Table 4). The reason for both observations might be that PMMA penetrates the blood-brain barrier less easily than PMA. The acute toxicity of PMA and PMMA is caused by the increased extraneuronal serotonin due to exchange diffusion and the inhibition of MAO-A which prevents the breakdown of serotonin. A hyperthermia-rhabdomyolysis syndrome then develops (Table 6). The hyperthermia reported in PMA fatalities was in the range of 42–46.1°C. The body temperature in volunteers taking MDMA in a dose range of 18–125 mg/70 kg changed by –0.17 to 0.65 °C (de la Torre et al., 2001). The hyperthermia may cause a perturbation of the cellular metabolism of calcium and cyclic AMP within the muscle fibres. In the case of a mitochondrial myopathy, the risk to develop hyperthermia increases (Larner, 1993). This has been concluded from clinical experience which shows that intoxication with MDMA and MDA can be treated with dantrolene.

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Table 6: Serotonin syndrome and symptoms after intoxication with MDMA and PMA

Serotonin syndrome (*)	MDMA intoxication (*)	PMA intoxication
Agitation	Agitation	Agitation
Delirium	Hallucinations	
Myocloni	Convulsions	Convulsions
Hyperthermia	Hyperthermia	Hyperthermia
Transpiration	Hypo- or hypertension	
Shivering	Tachycardia	Arrhythmia
Tremor	Mydriasis	
Diarrhoea	Rigor	Rigor
Ataxia	Coagulopathy	Disseminated intravascular coagulation
Hyperreflexia	Rhabdomyolysis	Rhabdomyolysis Tubular necrosis Hyperkalaemia Apnoea

(*) From Inserm, 1997.

Psychological risk assessment

Acute effects — effects on cognitive functioning

There is a report on the Internet, dated 26 July 2000, of individual subjects ingesting certain amounts of PMMA (<http://rhodium.lycaem.org/pharmacology/pmma.text>). While these are not scientifically controlled human trials, they are of certain evidential value. There are no other reports on the psychological effects of PMMA, besides the report of Shulgin and Shulgin (1991). The individual experiences described on the Internet are reported below.

Subject 1 (dose undefined): The subject was a female who suffered from insomnia, 'head noise' and temperature control problems.

Subject 2: The subject described the dehydrating actions of PMMA, which could affect his neuropsychological status. A further point to consider is the anorectic action of the amphetamines. The subsequent poor nutrition, with diminished absorption of vitamins, would affect the actions of any drug. The subject concluded from his own experience that the symptoms described by others in the Internet report 'are actually

caused by the malnutrition and dehydration that one puts their (*sic.*) bodies through during these extended periods of heavy use, and not so much (by) the drug’.

The subject found that if he avoided poor nutrition and hydration, he did not get any of the unpleasant side effects (e.g. nystagmus, stiffness of the body, cardiovascular stimulation, lack of sleep). He adds, ‘One other thing, if you start noticing some of the edginess or any of the jumpiness, pop a xanax, not a lot, about 0.25–0.50 usually does the trick. Within 20 minutes everything is just fine.’

Subject 3 (initial dose 50 mg): The subject describes the following experiences after a trial ingestion: after 15 to 45 minutes he experienced a ‘mildly speedy onrush, similar giddiness experienced when dosed with LSD mildly.’ After 1 to 1.5 hours he reported ‘some rolling of the eyes ... stimulated and yet relaxed to the point of not really wanting to do much but chill.’ At two hours he took 50 mg more PMMA and reported, ‘eye rolling increased and the desire to remain inactive increased.’ At four hours, sleep occurred automatically. On awakening, he wondered how and when he had got into bed.

In a second trial, this subject took 90 mg PMMA, with other people around for stimulation. He reported:

- Strange audiostimulation in which it seemed that sounds were all emanating from within his own head.
- The intent behind the words seemed more clear.
- He grew tired of idle, insignificant conversations and went to bed.

In a third trial, he ingested 110 mg PMMA. The initial stimulation lasted about one hour, turning into a ‘who needs to work’ attitude which was fairly persistent. He noticed his skin crawled with strange cold tingling sensations which were rather pleasant. His mental ‘wheels’ turned very slowly. He experienced no anxiety whatsoever, and felt ‘almost too calm’.

He concludes, ‘at the <50 mg level, PMMA serves as a nice stimulant similar to ginseng. It also seems to blur out emotional turmoil. Motivation seems a bit diminished. In comparison with MDMA, PMMA seems to lack the super rush of MDMA in the initial onset. The feeling of being out of control and at the mercy of the drug was not present. The down time is nowhere near that of MDMA.’

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Subject 4 (215 mg dose): This subject reports 'After 45 min I returned to rolling, hard. My jaw went into total lockdown and my eyes began to cross, weird as hell. Euphoria was there. The experience was very similar to MDMA. (Six hours later) I am in a stupor.'

The next day he took the same dose with the same experience. The day after he was a little disoriented. He found himself much more introspective and emotional than for previous post-dosage days (e.g. crying for very little reason). He also noticed a jumpiness of a reflex-type nature.

He considered that PMMA was active in a psychedelic way at these dosages. An amphetamine component was not really present. It was very difficult on the body as recovery was very slow.

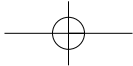
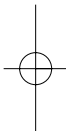
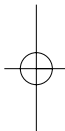
Subject 5: This subject observed that the dose response curve for PMMA can, in some subjects, be very steep. At 100 mg, the subject experienced very mild, relaxing, euphoric effects that were physically pleasant. But when 150 mg was ingested some weeks later, there were severe physical ill effects. The acute effects were transpiration, tremor, severe nystagmus, the subject's body became very stiff, and his head and stomach hurt badly. There was no anxiety and the pulse did not rise. The head and neck turned very red. The jaw felt locked but there was no clenching as with MDMA. There was a great pressure over the chest and some nausea. After two hours, the physical terror had begun to decline. The subject reported of PMMA that 'it is not psychedelic.'

Shulgin and Shulgin (1991) reported that, after an oral dose of 110 mg, there was none of the central effects of MDMA. He comments, 'The active components are primary amines and the N-methyl homologues might have, in general, the stimulant component maintained, but the psychedelic contribution is generally much reduced. MDMA is, of course, an exception.'

The psychological effects of PMA have been described by Shulgin as follows: 'I found the effects of 60 mg reminiscent of N,N-diethyltryptamine, distinct after-images, and some paraesthesia. I was without any residue after five hours. With 70 mg it hit suddenly. I had a feeling of druggedness (*sic.*), almost an alcohol-like intoxication, and I never was really high in a psychedelic sense.'

Shulgin wrote that, in human trials conducted 20 years ago in which the mechanism of the psychosis-inducing action of dexamphetamine was explored, PMA did not produce a psychotic state at the highest dose used (75 mg). He added, 'PMA produced excitation and other central effects, it produced adrenergic pressor effects, and it consistently produced measurable quantities of PMA in the urine, but no amphetamine-like crazies.'

There are no other reports available concerning the psychological risk assessment of PMMA.



Chapter 5

Sociological and criminological evidence on the risks of PMMA

Introduction

Sociological evidence on the effects of PMMA is limited by the fact that there is no evident consumer market for this drug in Europe. In those cases where PMMA has appeared on the European market, it has always been consumed with PMA, as part of a tablet which was believed to be 'ecstasy' ⁽¹⁵⁾. Thus, this chapter is limited to a few brief sociological observations on the following:

- The social aspects of, and items of concern regarding, the content of 'ecstasy' tablets.
- Some Internet illustrations of the retail market for new synthetic drugs.
- Some implications for the media and policy-makers.

Europol has contributed evidence on the wholesale production and distribution of PMMA.

Social consequences: the fear of health risks and the development of knowledge

Recent deaths that have occurred from PMMA/PMA in four northern European Member States, together with media reports of dangerous new synthetic drugs, have fuelled growing concerns about dangerous products on the 'ecstasy' market. Fears of adulteration are not supported in substantial numerical terms by forensic analysis. Nevertheless, there is evidence of an active and growing commercial market in 'ecstasy' testing kits (e.g. 'E-Ztest', 'DanceSafe', 'Pro-test'). The existence of this commercial market implies that there is a demand for scientific knowledge about pill contents, albeit that this demand may come from the dealers/consumers of 'ecstasy'. Drug user orientated Internet web sites and drug newsgroups are also becoming an increasingly important source of rapid information about the risks and benefits of new synthetic drugs.

⁽¹⁵⁾ The term 'ecstasy' is synonymous with MDMA because, in general, MDMA is the drug that is most often found in tablets sold as 'ecstasy'.

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Research shows that for many 'ecstasy' users, knowledge of the range of brands, a perceived ability to distinguish between brands, to link nomenclature to differing effects, and to have favourite brands, were all part of a broader process of demonstrating maturity and familiarity with the drugs scene (McElrath and McEvoy, 2001). The social importance of demonstrating knowledge is illustrated in ethnographic research and Internet newsgroups. For example, in a recent Internet newsgroup discussion, a participant made the observation that the deaths that have occurred from PMA were among people who took large doses of PMA (over 100 mg), expecting to experience MDMA effects. He/she added that, in their personal experience, '30 mg of PMA mixed with 50 mg MDMA feels like 150–200 mg MDMA. Do not throw this pill away...MDMA + PMA is an excellent mix, may well be one of the best pills you ever have!' ('alt.drugs ecstasy' newsgroup, August 2001).

Another newsgroup participant observes that the effects of PMA are particularly good when mixed with MDMA but that 'PMA when taken by itself is quite horrible' ('alt.drugs ecstasy' newsgroup, July 2001).

The presence of 'ecstasy' as an integral part of the music and dance scene has created a 'platform of acceptability' among substantial numbers of young people who may now be willing to experiment with all manner of drugs to serve fashionable recreational purposes (Shapiro, 1999).

The retail market

Criminological evidence about the wholesale production and distribution of PMMA and PMA is covered in Europol's contribution (below). Internet newsgroups also provide some insights into consumer demands and the retail market. Interest in health issues and avoiding harm from new synthetic drugs is evident in Internet discussions. Newsgroups suggest that criminal suppliers are, in general, careful not to distribute drugs that will prove unpopular because of health risks.

A regular participant in the 'alt.drugs ecstasy' newsgroup recently provided the following description of the retail market in 'ecstasy' pills:

As soon as a pill is known in the scene as bad, no one can sell that kind anymore, and every dealer then calls their dealer, and gives them back ... So in about 8 hours

time, the pills go all the way down the chain, and all the way back ... the dude at the top takes unsellable pills back, which all the ones I've ever heard of do ... Once you get a reputation from those who 'know you' that you sell bunk/bogus pills people stop buying from you ... I know one person who has been sitting on roughly 2 000 yellow bananas for the past three months and can't get rid of them (Golaszewski, 2000).

The consequences of prohibition and law enforcement activity are other aspects of new synthetic drug supply addressed in Internet discussion groups. For example, in relation to PMA, some postings have observed that restricting sales of MDMA precursors has prompted underground chemists to produce PMA to ease availability ('alt.drugs psychedelics' newsgroup, 2001; 'alt.drugs ecstasy' newsgroup, 2001).

Implications for the media and policy-makers

Newspapers and television play a major role in providing information for the general public about drugs and in shaping public opinion (Farrell, 1989; Coomber, 2000). When a new synthetic drug is reported in the press, journalists tend to use 'ecstasy' as a reference substance, describing the new drug in terms of its relative potency compared with 'ecstasy'. In view of the growing disenchantment with 'ecstasy' that has been reported in the EU among frequent and heavy users, journalistic references to 'extra strong', 'more potent' forms of 'ecstasy' may promote an image of the new drug that makes it desirable for particular groups of drug users. Promoting a desirable image is counterproductive for policy-makers concerned with preventing drug use. Careless press reports of the relative safety of PMMA, with regard to long-term neurotoxicity, may also be counterproductive, for the same reasons.

Theories about diffusion of innovation suggest that 'opinion leaders' play a significant role in influencing the development of new drug trends (EMCDDA, 1999). In the field of new synthetic drugs, Alexander Shulgin may be viewed as a significant opinion leader for potential consumers. It is worth noting that in his answer to an Internet question about the danger of PMA, he replied that:

PMA is a rather dangerous drug in the rave scene. At 60 or so milligrams orally it is a stimulant and modest turn on. At a two-pill dose, twice this dosage, it becomes a strong stimulant and is a threat to the cardiovascular system. But people at raves can be seen taking six pills at a time, and with PMA this puts them in a dangerous place,

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one that can be lethal. Be careful — this is a potentially damaging drug
(<http://www.alchemind.org/shulgin>).

With regard to PMMA, in his book, 'Pihkal', Shulgin concluded that human experimentation should be discouraged adding that, 'I tried it and I didn't like it' (Shulgin and Shulgin, 1991).

Recent social research on the prevention of 'ecstasy' use concludes that information should be accurate and up to date, with a focus on relevance. Researchers also advocate that detailed information should be specifically targeted and made available through appropriate means. For example, when information is for 'ecstasy' users, it should be provided in dance venues and provided by peer educators. Research also concludes that dance and music venues should also be appropriately designed, managed and staffed (McElrath and McEvoy, 1999; Malberg and Seiden, 1998).

Wholesale production and distribution ⁽¹⁶⁾

Involvement of international organised crime

Contributions of Member States' law enforcement agencies

Europol twice requested the Europol national units to supply information on PMA/PMMA:

- In May 2001, in order to draft the 'Joint EMCDDA–Europol progress report on the joint action on new synthetic drugs', as requested by the horizontal working party on drugs.
- In September 2001, following the decision of the horizontal working party on drugs to request the EMCDDA to carry out a risk assessment as provided for under Article 4 of the joint action on new synthetic drugs.

Information provided by the Member States enabled Europol to report on seizures of tablets that contained:

⁽¹⁶⁾ Europol's contribution to the risk assessment.

- PMA, and in some cases other active substances, but not PMMA.
- PMMA but not PMA (no such seizures were reported).
- Both PMA and PMMA and, in some cases, other active substances.

PMA

Finland, Greece, Ireland, Italy, Luxembourg, Portugal and Spain have reported that their law enforcement agencies did not seize PMA, nor do they have any information on the production, distribution and trafficking of the substance or on the role of organised crime in these activities. In Belgium, France, Germany, Sweden and the UK, small seizures of tablets containing PMA occurred; in the Netherlands, there were five seizures totalling 5 374 tablets of PMA. These seizures are summarised in Table 7.

Table 7: Overview of seizures of PMA/PMMA in the Member States as reported to Europol (until October 2001)

Member State	Number of tablets	Logo	Active substance		
			PMA	PMMA	Other
Austria	1	'E'	*	*	
	1 785	'Mitsubishi'	*	*	Amphetamine
	2 693	'Mitsubishi'	*	*	
	10 000	'E'	*	*	
Belgium	X	xTc	*		
Denmark	1	'Mitsubishi'	*	*	
	1	'Mitsubishi'	*	*	
	1	'Mitsubishi'	*	*	
	4	'Mitsubishi'	*	*	
	68	'Mitsubishi'	*	*	
	78	'Mitsubishi'	*	*	
	83	'Mitsubishi'	*	*	
	155	'Mitsubishi'	*	*	
	718	'Mitsubishi'	*	*	
	843	'Mitsubishi'	*	*	
	25	'Mitsubishi'	*	*	
X	'Mitsubishi'	*	*		
X	'Mitsubishi'	*	*		

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Member State	Number of tablets	Logo	Active substance		
			PMA	PMMA	Other
France	1	No logo	*		MDA and chloroquine
	1	No logo	*		MDA and chloroquine
	1	'Superman'	*		MDMA
	1	'Superman'	*		MDMA
	1	'Superman'	*		MDMA
	1	'Superman'	*		MDMA
	1	'Superman'	*		DMA
Germany	3	'Mitsubishi'	*	*	Ephedrine
	5	'Mitsubishi'	*	*	Ephedrine
	10	'Mitsubishi'	*	*	Ephedrine
	18	'Elephant'	*		MDMA
	8	'Elephant'	*		MDMA
	17	'Mitsubishi'	*	*	
	337	'Jumbo'	*	*	
224	'Mitsubishi'	*	*		
Netherlands	27	'Elephant'	*		
	119	'Elephant'	*		
	5 000	'Elephant'	*		
	14	'Mitsubishi'	*		
	214	'Nike'	*		
Sweden	1	'Mitsubishi'	*	*	Amphetamine
	1	'Mitsubishi'	*		Methamphetamine
	2	'Mitsubishi'	*		
	2	'Mitsubishi'	*	*	Amphetamine
	3	'Mitsubishi'	*	*	
	4	'Mitsubishi'	*	*	Methamphetamine
	8	'Mitsubishi'	*	*	
	19	'Mitsubishi'	*	*	
1 782	'Mitsubishi'	*	*	—	
United Kingdom	14	'Elephant'	*		
	57	'Nike'	*		

PMMA

No Member State has seized tablets that contained only PMMA as an active substance.

PMA/PMMA

In Belgium, Greece, Spain, France, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Finland and the UK, no seizures of PMMA/PMA tablets occurred, nor is there information on the production, distribution and trafficking of these substances or on the role of organised crime in these activities.

The Europol national units of four Member States (Denmark, Germany, Austria and Sweden) have reported seizures of PMA/PMMA tablets to Europol. The seizures are mentioned in Table 7. In all but one case, these tablets had the 'Mitsubishi' or 'E' logo. In one case, 337 tablets with the 'Jumbo' logo and containing PMA/PMMA were seized in Germany.

The Austrian Europol national unit reported the seizures of 4 478 tablets with the 'Mitsubishi' logo and active substances PMA and PMMA. The tablets were part of a 5 000 tablet shipment, which was obtained from a Polish citizen. A further, 10 000 tablet shipment was planned for September 2000. On 17 October 2000, a Polish citizen was arrested after supplying 10 000 tablets with the 'E' logo and the active substances PMA and PMMA. These tablets were smuggled by car from Poland to Austria.

The Belgian Europol national unit has no information on production, trafficking and distribution of PMMA in the country. However, in 2001, four people died due to overdoses of PMA.

The Danish Europol national unit reported 13 seizures of tablets with PMA/PMMA in 2000 and 2001, varying between 1 and 843 tablets. Danish Police suspect that all seizures probably relate to a single importation of some 18 000 tablets, in June 2000, by a Danish suspect who, through an associate who was arrested in Austria, had contacts with Polish criminals.

The German BKA reported two seizures of tablets with PMA as the active substance and another six seizures of tablets containing PMA and PMMA. Four seizures were made after a person died of the abuse of one or more tablets and one victim died after taking five tablets. Follow-up investigations led to the arrest of a supplier in possession of 18 tablets containing PMA and MDMA, in addition to a further 974

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'ecstasy' tablets, 100 LSD trips, 10 g of amphetamine and 7 g of herbal cannabis. The 18 tablets seized were part of a delivery of 1 000 tablets with the logo 'Mitsubishi'. In December 2000, two German nationals were arrested for possession of 337 tablets with the 'Jumbo' logo and another 224 tablets with the 'Mitsubishi' logo. The tablets contained PMA and PMMA and were obtained in the Netherlands. The BKA also received information from the French OFDT (Observatoire Français des drogues et des toxicomanies) relating to the analyses of seven samples (five tablets with the logo 'Superman' and two powders) from seven investigations. PMA was detected in all samples.

The Dutch Unit for Synthetic Drugs reported the seizure of 119 tablets containing PMA, on 25 October 2000, with the logo 'Elephant'. After an exchange of information with the German authorities, Dutch law enforcement agencies seized a further 5 000 tablets with the 'Elephant' logo and containing PMA and MDMA, in January 2001. According to the German BKA, there was no forensic link between the seized tablets with the 'Elephant' logo and the 'Mitsubishi' tablets.

The Swedish Europol national unit reported a total seizure in 2000, in nine incidents, of 1 819 tablets that contained both PMA and PMMA. Amphetamine and/or methamphetamine were present in seven of these tablets. Another three tablets only contained PMA. In eight of the cases, seized quantities varied between 1 and 19 tablets. During a house search in Stockholm, 1 782 PMA/PMMA tablets were seized following surveillance of members of a criminal group of Polish origin. There are no indications for production of PMA and/or PMMA in Sweden.

Investigations by the BKA, including forensic analysis in the framework of their CAPE (Chemical analysis programme 'ecstasy') system, have established a connection between seizures of PMA/PMMA tablets in Austria, Canada, Denmark, Germany, Poland, Sweden, and the USA. In December 2000, Polish authorities raided two illicit laboratories resulting in the arrest of four persons. Inside these laboratories equipment, including tableting machines and chemicals, were found. According to the Polish authorities, production of PMA and/or PMMA continues to take place in other laboratories in the country and in the Ukraine.

Conclusions

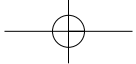
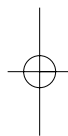
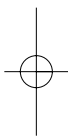
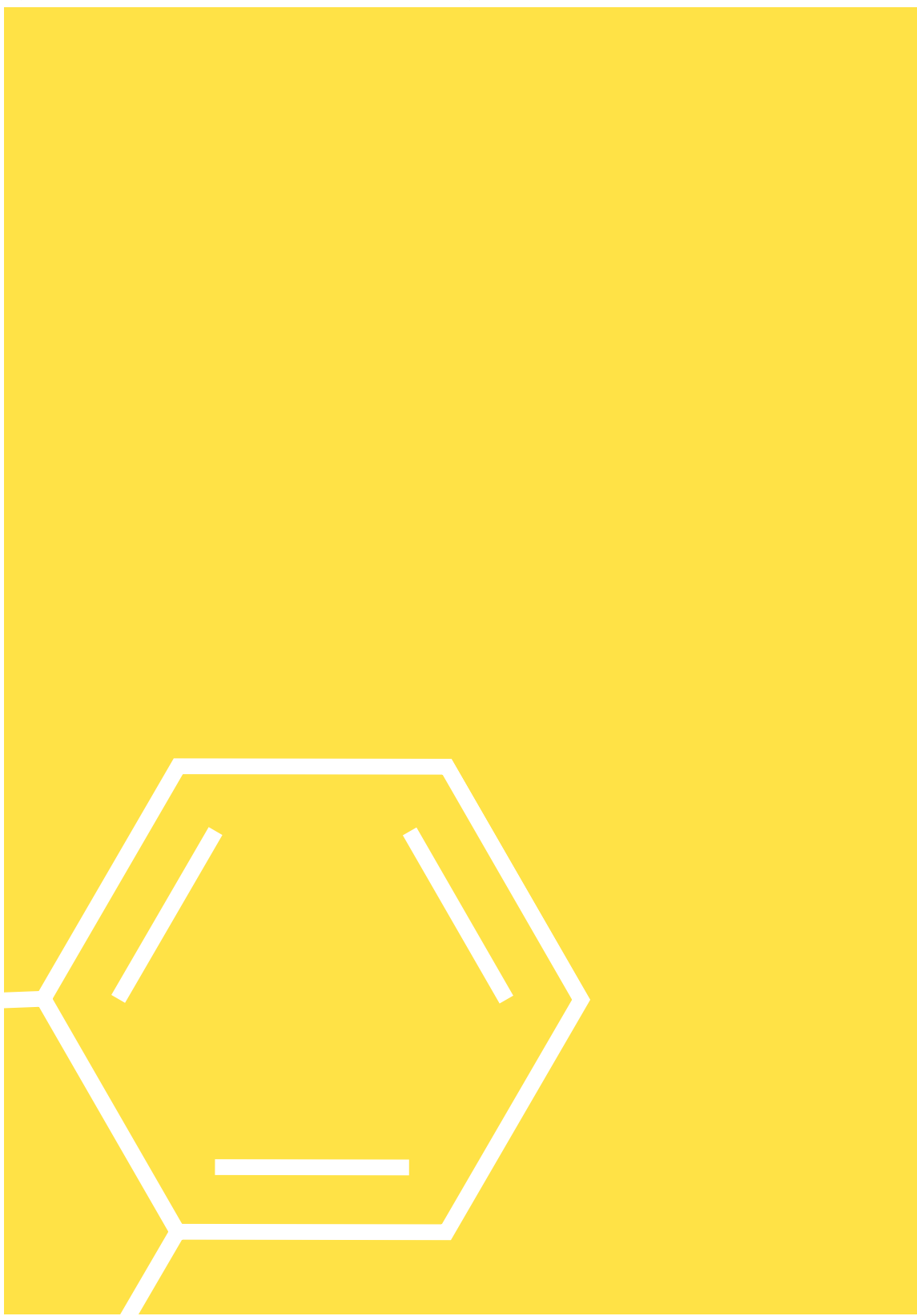
- Distribution of PMA has taken place in six Member States: Belgium, Germany, France, the Netherlands, Sweden and the UK. This relates to the seizure of some 5 480 tablets in 19 incidents.
- Trafficking and distribution of PMMA has taken place in four Member States: Denmark, Germany, Austria and Sweden.
- In all cases where PMMA was seized (18 870 tablets in 29 incidents), the tablets also contained PMA and had either the 'Mitsubishi' logo or the 'E' logo, with the exception of 337 tablets with the 'Jumbo' logo.
- The total amount of seized PMA and PMA/PMMA tablets in the Member States in 2000 is relatively small when compared to overall 'ecstasy' seizures in the EU (17 426 531 tablets in 2000).
- Large-scale production of PMA or PMMA does not occur in any Member State.
- Three Member States, Denmark, Austria and Sweden, have information on the role of organised crime in the trafficking of PMA/PMMA. This relates to criminal groups from Poland. These findings, combined with links established by the BKA, and the fact that the Polish authorities seized two illicit laboratories for the production of PMA and PMMA, lead to the conclusion that PMA/PMMA tablets seized in the Member States, Canada and the USA, are likely to have originated in Poland.
- Since seizures of PMA/PMMA tablets in 2001 in the Member States probably relate to importation in 2000, production of PMA/PMMA tablets may have stopped, at least temporarily, following the dismantling of two illicit PMA/PMMA laboratories in Poland in December 2000.

Money laundering aspects

No reliable data are available on the volume of money laundering in relation to the production and trafficking of PMA/PMMA.

Violence in connection with wholesale production and distribution

The Member States did not provide data on violence in connection with production and distribution and trafficking of PMA/PMMA.



Chapter 6

Public health risks of PMMA: epidemiological evidence

Introduction

PMA has been listed as a controlled drug in the UN Convention Schedule since 1986. It first appeared on the illicit drug market between 1972 and 1973 in the USA and Canada and was usually sold as 'ecstasy'. It acquired the street name 'death' because of its link to at least nine deaths (Cimbura, 1974; Stafford, 1992; Shulgin and Shulgin, 1991). In the second half of the 1990s, PMA was identified as causing at least six deaths in Australia (Felgate et al., 1998; Byard et al., 1998). PMMA appeared in Europe in 2000, and the epidemiological evidence is closely linked to that of PMA because, with the exception of Spain, PMMA has always been found combined with PMA in tablets sold as 'ecstasy'. The CAM in the Netherlands conducted a risk assessment of PMA and PMMA combined on 5 October 2001 (Reitox national reports).

The epidemiological evidence presented here regarding the public health risks of PMMA/PMA, is based on information collected from:

- i. Reitox national focal points in 15 EU Member States
- ii. Europol report
- iii. Published social science and medical literature
- iv. The Internet (English language searches)
- v. Youth and mass media (English language searches)

Numbers from the list above are used in the text to code the sources of information.

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The availability and quality of the product on the market

Availability at the consumer level (i and ii)

In Europe, there appears to be no evident consumer market for either PMA or PMMA. PMMA was first identified by the laboratory analysis of tablets and body fluids in 2000. It has always been found together with PMA, with the exception of one report from the Spanish national focal point. With regard to large seizures, four Member States (Denmark, Germany, Austria and Sweden) reported nine large seizures of PMMA together with PMA in tablets consumed as 'ecstasy' between June 2000 and July 2001. The Netherlands reported three large seizures of tablets containing PMA with MDMA or MDA and two seizures of tablets containing PMA without MDMA or MDA. With regard to small seizures, 'ecstasy' tablets containing PMA and/or PMMA have been reported in eight Member States (Belgium, Germany, Spain, France, the Netherlands, Austria, Sweden and the UK) as well as in Norway and Poland.

The 'Mitsubishi', 'Jumbo' or 'E' logo are the most common logos found on tablets containing PMMA/PMA. Other tablets containing PMA, but no PMMA, have carried 'Mitsubishi', 'Elephant', 'Nike', 'Superman', and 'xTc' logos.

Recent laboratory analyses of tablets sold as 'ecstasy' from law enforcement seizures, or pill-testing projects, show that MDMA is the most common substance found in tablets sold as 'ecstasy'. For example, in the Netherlands in 1999, 86 % of analysed tablets sold as 'ecstasy' contained MDMA (EMCDDA, 2001c). The MDMA content, however, is variable ranging from less than 30 mg to over 120 mg.

The availability of 'ecstasy' testing kits sold commercially on the Internet indicates a demand for better knowledge about the contents of tablets, although this demand may be largely from dealers. In September 2001, the 'E-Ztest' web site began to sell a new colour change test that claims to detect PMA, but not PMMA, at a cost of EUR 35. The 'E-Ztest' site warns 'ecstasy' users against PMA and gives detailed description of expected colour changes related to primary or secondary amines. The site claims high levels of sales, and offers information in different languages and currencies, with discrete mailing. The 'E-Ztest' site claims it has been selling tests kits for three years to more than 100 different countries (<http://www.eztest.com/index>). The site links to a 'pill reports' site and publishes a 'subjective' list of pill content reports from North

America, Europe and Australia. According to this list, in September 2001, out of 100 different 'ecstasy' tablet reports, only one tablet was being marketed with a 'PMA' logo. This 'PMA' tablet was identified in Adelaide, suggesting that there may be a small market specifically for PMA in Australia.

Sources at the consumer level (i and ii)

Research among recreational drug users in dance and nightlife settings show that whilst friends are probably the most usual source of 'ecstasy', retail dealers and dealer users also operate. In the Netherlands, research has shown that 64 % of 12–18 year-olds purchased 'ecstasy' from friends, 15 % in cafes and bars and 35 % from home delivery (Reitox national reports, EMCDDA 2001c).

Trends in availability (i and ii)

Very little information available. PMA first appeared in the USA and Canada in 1972 and PMMA appeared with PMA in the northern European dance scene as 'ecstasy' in 2000.

Average dose, degree of variability, purity levels and presence of adulterants (i, ii and iv)

Limited data on content of PMA and PMMA are presented in the pharmacological report, which shows the variability between the tablets containing PMA.

With regard to the reaction of PMA and PMMA to colour change tests, two samples analysed by GC-MS, which identified PMA and PMMA, produced no reaction for the Marquis colour test. They gave a positive result for the nitroprusside colour test and a colour change of purple to brown for the Liebermann colour test (*Microgram*, 2001). Another report based on tests conducted in the 1960s states that neither PMA nor PMMA give a short-term response (<30 seconds) to Marquis reagent. Like MDMA, PMMA gives the positive blue colour of a secondary amine, while PMA does not elicit a colour (Dal Cason, 2000).

Anecdotal evidence suggests that there is little financial incentive for illicit suppliers in tablets perceived as poor quality.

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Other active ingredients (ii)

In the Netherlands, a large number of tablets containing a mixture of PMA and MDMA have been seized (Europol contribution).

Typical prices (i and iv)

Street level prices of 'ecstasy' ranged between EUR 6.4 and EUR 25 per tablet (EMCDDA, 2001c). In August 2001, a popular Italian Internet site (<http://www.fuoriluogo.it/quotazioni>) provided a narrower range of prices of between EUR 8 and 19, with Amsterdam, Florence, London and Milan all around EUR 15 for one tablet.

Knowledge, perceptions and availability of information

Availability of scientific information (i and iv)

There is considerably more scientific information about PMA than PMMA. Specific information about the dangers of PMA is available in a variety of forms including peer education, outreach work, leaflets, youth media, television, newspapers and the Internet. New information about deaths linked with PMA has rapidly been made available on web sites concerned with illicit drug use and pill testing. For example, in August 2001, the 'E-Ztest' site provided early information about deaths linked to PMA in Belgium and provided links to a range of Belgian and Dutch newspaper reports about the deaths (<http://www.eztest.com>).

Availability of information on effects of product (iv)

Information about the effects of PMA is widely available on Internet sites targeting recreational drug users. Information frequently includes the dangers of taking more than 60 mg and the effect of PMA on raising body temperature (<http://www.alchemind.org/shulgin>).

Level of awareness of product amongst drug consumers in general (iii)

No evidence available.

Level of knowledge of product, effects and perceptions amongst consumers of product

As there is no market for PMA/PMMA, there is no evidence from deliberate consumers. However, it is worth noting that a study of 'ecstasy' users in Northern Ireland showed that consumers of 'ecstasy' perceive the brand/logo as a useful means to distinguish between good and bad tablets and believe that the logo helps to identify the specific types of effects that one should expect from a particular brand. Only a few respondents believed otherwise (McElrath and McEvoy, 2001). This belief in the significance of logos exists despite forensic evidence that there is at least some variation in the content found in tablets carrying the same logo and warnings about PMA having been identified in tablets carrying the 'Mitsubishi' logo, for example. The Northern Ireland study found that particular brands/logos appeared to produce the same physical or psychological effects for all or most users within a particular friendship or drug-using network in the same setting. Furthermore, 'ecstasy' users described a range of pharmacological and social expectations about the effects of the drug. They expect to feel 'loved up', 'sociable' and 'confident' and the way in which those feelings are best manifested is in the user's interactions with others. In-depth studies such as this demonstrate that the drug's capacity to deliver is realised through setting and this serves a purpose for illicit producers to use the logos as a marketing device.

Illegality is not an issue for most regular consumers who tend to question the credibility of government and media messages about drugs. Young people tend to obtain information about drugs from other sources, namely through personal experience or from friends and acquaintances. (McElrath and McEvoy 1999; Winstock et al., 2001).

General population

It is unlikely that many people in the general population have heard of either PMA or PMMA.

Television and newspapers are a major source of information about illicit drugs, or a stimulus for discussion among the general public, and newspaper reports of 'ecstasy' deaths usually exaggerate the potential for acute damage to health. Consequently, among the general and school age population, 'ecstasy' is widely perceived as carrying high risks for health (EMCDDA, 2001c).

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Prevalence and patterns of use

In view of the fact that PMA/PMMA is consumed as 'ecstasy', the prevalence data for 'ecstasy' is relevant (EMCDDA, 2001c). Overall, 0.5–4 % of European adults have tried 'ecstasy' and most of this use is concentrated in particular groups with a high affinity for recreational drug use. These figures, viewed in the light of the very limited number of PMA/PMMA seizures (60 in total) compared with 16 000 for 'ecstasy' in Europe overall, indicate that prevalence of PMA/PMMA consumption is extremely restricted.

The only other indicators of prevalence are three reports of PMA being detected in urine samples in 2001 (one in Austria and two in Belgium)(Reitox national reports).

Frequency of use (iii)

A large European survey found that only 4 % of young people in recreational nightlife settings took 'ecstasy' more than once a week (Calafat et al., 2001). Small proportions of these young people consume several tablets during one episode, at least at some point during their drug career. Although heavy consumption is usually confined to a short period, it is these people who are at the greatest acute and long-term health risks from both MDMA and PMA/PMMA (Korf and Lettnick, 1994; McElrath and McEvoy, 1999). Particular settings invoke more intensive forms of drug use, for example, both the frequency and amount of drugs used tends to increase during holiday periods (Bellis et al., 2000).

Route(s) of administration (i, ii, iii)

PMA/PMMA are usually taken orally, in the form of tablets sold as 'ecstasy' (Reitox national focal points and Europol). Following the patterns of using 'ecstasy', a tablet containing PMA/PMMA may involve taking an initial dose, followed by a smaller dose after about one and half hours. In the case of MDMA, this is done in order to prolong the positive effects with only a modest exacerbation of the usual physical side effects (Shulgin and Shulgin, 1991).

Other drugs used in combination with the product (iv)

Participants in Internet newsgroups have observed positive effects from mixing PMA with MDMA and negative effects from mixing PMA with alcohol ('alt.drugs.ecstasy' newsgroup).

Geographical distribution of use (i and ii)

Evidence about the geographical distribution is very limited but it should be noted that, among the recent deaths, all four that were linked to PMMA occurred in Denmark and in Austria. Seizures of PMA/PMMA, and deaths from PMA, have all occurred in Northern European States (Belgium, Germany, France, the Netherlands, Norway, Sweden, and the UK) with the exception of a national focal point report from Spain (Reitox national focal points and Europol).

Trends in prevalence and patterns of use

Countries such as the UK, Ireland, and the Netherlands may be experiencing a plateau effect with 'ecstasy' or even a downturn. Some researchers have noted an increase in the use of a range of substances to augment the positive effects of 'ecstasy', known in the Netherlands as the 'combi-high' (Nabben and Korf, 2000; Lecesse et al., 2000).

Characteristics and behaviour of users

Age and gender of users (iii)

Evidence suggests that age, and where people live, are more significant than gender in relation to taking 'ecstasy' and therefore, inadvertently, to taking PMA/PMMA. However, there is anecdotal evidence that males are more likely to use 'ecstasy' excessively and be less concerned about harmful effects than female users (Collison, 1996; McElrath and McEvoy, 1999).

Social groups where product available/used (iii)

Most research on 'ecstasy' use has linked it with the techno dance and nightlife scene and linked the sought after effects to appreciation of the music, dance and socialising (EMCDDA, 1997; Calafat et al., 2001).

Risk behaviour associated with use (iii)

The greatest risk behaviour associated with use is taking PMA/PMMA as if it was MDMA. People who take more than one tablet over a short time period are at greatest risk of both acute and long-term health problems from both MDMA and PMA/PMMA.

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Special concerns about vulnerable groups (iii)

Special concerns relate to the lack of knowledge both about drug content and about the specific harmful effects of PMA and PMMA. One group of young people who are particularly vulnerable are heavy, excessive, users who belong to groups that are at high risk for a range of problems (Collison, 1996; McElrath and McEvoy, 1999).

Trends in characteristics/behaviours of users (iii)

Research has shown that people tend to use 'ecstasy' as long as the positive factors outweigh the negative; the illegality of a drug is not a significant factor among 'ecstasy' users (EMCDDA, 2000). A study of 'ecstasy' users in Northern Ireland found that the vast majority of respondents reported that they would stop using 'ecstasy' if most or all of their friends did (McElrath and McEvoy, 1999).

Indicators of health consequences

Health risks appear to be more closely related to patterns of heavy or frequent use than they are to the drug content of individual tablets.

Hospital emergencies (iii)

In mid-2001, a paper was published in the *Medical Journal of Australia* describing the clinical features of PMA poisoning (22 cases). It concluded that, in the Royal Adelaide Hospital, PMA poisoning accounted for most of the severe reactions among people who believed they had taken 'ecstasy'. The authors advised that PMA toxicity should be suspected with severe or atypical reactions to 'ecstasy' (Ling et al., 2001). Wide dissemination in Europe of these Australian findings may influence the processes of toxicological analysis in hospital emergencies related to 'ecstasy'. PMA/PMMA may increasingly be recorded as linked to cases presenting as 'ecstasy' intoxication, which previously would have been linked to MDMA.

Deaths (direct and indirect)(i and ii)

Since 1995, PMA has been implicated in at least eight deaths in Australia and 10 in the USA. In Europe, according to the Spanish national focal point, one death in Spain in 1993 was linked to PMMA and another, in 1995, was linked to PMA. Between July 2000 and October 2001, there were ten deaths reported as linked with PMA alone

or combined with PMMA in the EU. Three deaths linked to a mixture of PMMA and PMA occurred in Denmark and one occurred in Austria. Six other deaths were reported as linked to PMA and no PMMA, two in Germany and four in Belgium. In at least five deaths, more than one tablet had been taken. In one death, at least six other drugs had also been taken (MDMA, MDA, amphetamine, cannabis, codeine and alcohol; solvents were also suspected) (Reitox national focal points, Table 5).

Initially, a Belgian fatality in February 2001 was recorded as being caused by a toxic concentration of MDMA (0.7 µg/mg) combined with amphetamine. In subsequent investigations, as part of a research project some months later, PMA 1.43 µg/mg was found in blood samples from this person. Subsequent investigations for PMA may have been prompted by heightened awareness of the potential role of PMA in 'ecstasy' intoxication.

Traffic accidents

No evidence available.

Requests for treatment/counselling

No evidence available.

Other health indicators

No evidence available.

Context of use

Risk factors linked to circumstances and rituals of consumption

The main risk factor has already been addressed and relates to taking PMA/PMMA unknowingly as if it were MDMA.

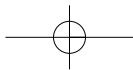
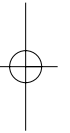
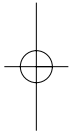
Implications for the non-using population (i and iv)

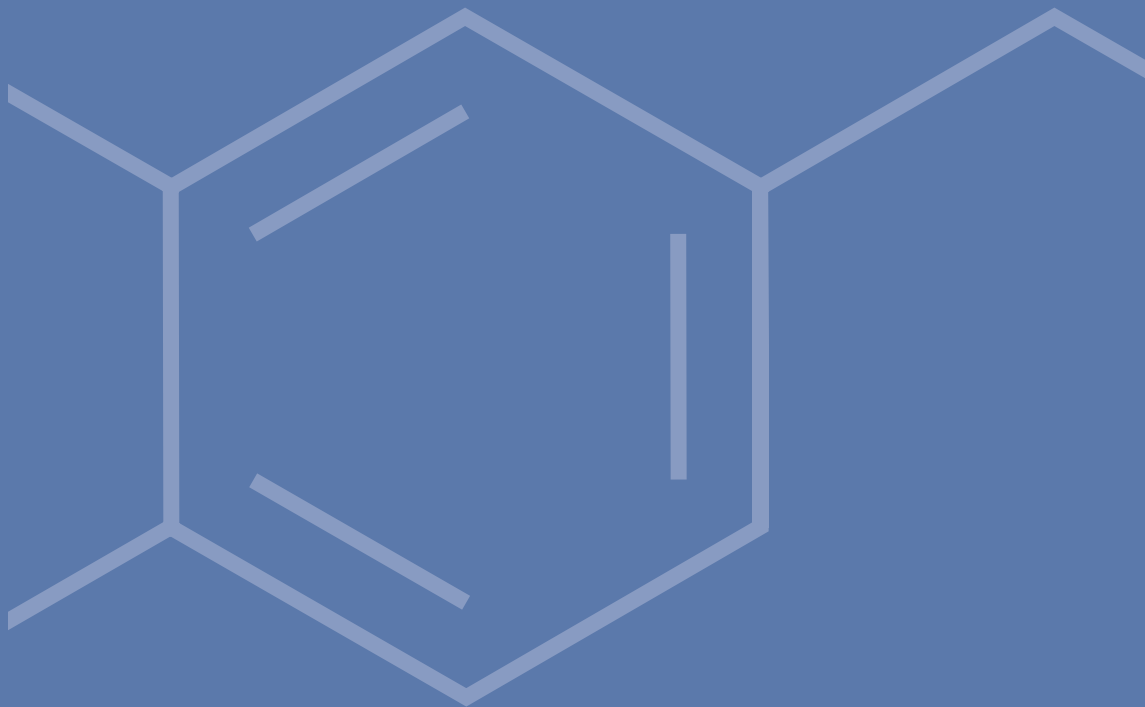
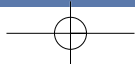
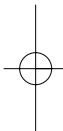
Increasing concern about the possibility of long-term harmful effects of MDMA may make the use of other new synthetic drugs, which are less neurotoxic, an attractive alternative for MDMA. Also, for regular 'ecstasy' users who perceive a need to

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increase the dosage in order to get positive effects with MDMA, combining MDMA with PMA may appear to be an option ('alt.drugs.ecstasy' newsgroup).

Fears among the 'ecstasy' using population about consuming PMA/PMMA unknowingly may serve to reduce consumption of 'ecstasy'. However, research shows that when one form of drug consumption is curtailed another frequently replaces it (McElrath and McEvoy, 1999). For example, it has been suggested that there is a growing trend in cocaine use among former 'ecstasy' users, as result of their disenchantment with 'ecstasy' and fears about long-term neurotoxicity (EMCDDA, 2001c).





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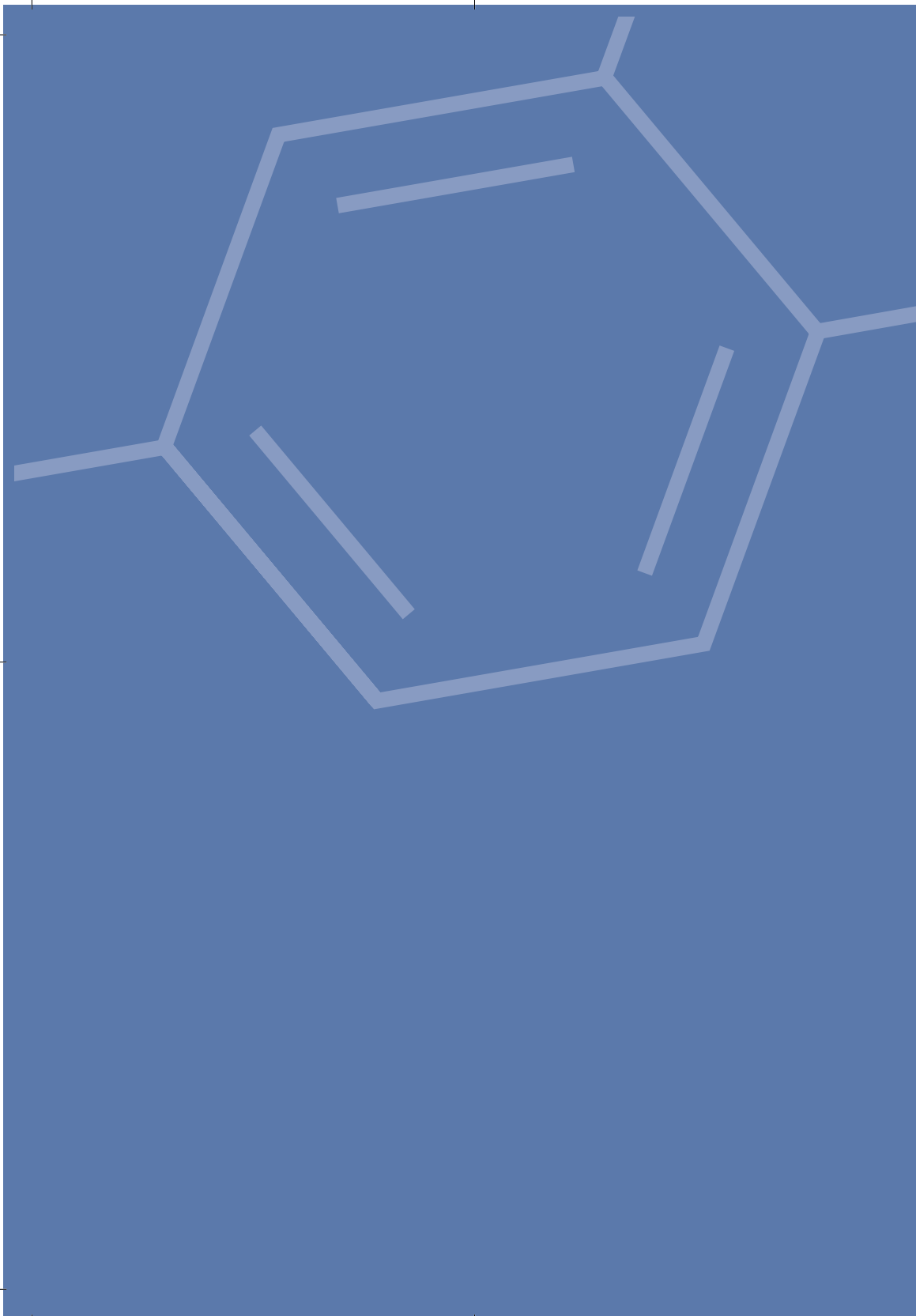
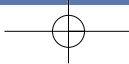
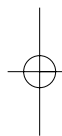
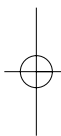
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Participants in the risk assessment process

EMCDDA Scientific Committee

Members

Prof. Salme Ahlström, National research and development centre for welfare and health, Helsinki, Finland

Dr Robert Wennig, Laboratoire National de la Santé, Centre Universitaire du Luxembourg, Luxembourg

Dr Desmond Corrigan, School of pharmacy, Trinity College, Dublin, Ireland

Dr Sheila Bird, MRC Biostatistics unit, Institute of public health, University Forvie Site, Cambridge, UK

Dr João Goulão, Drug addiction prevention and treatment service, Ministry of health, Lisbon, Portugal

Dr Katerina Matsa, Psychiatric unit 18 ANO, Psychiatric hospital of Athens, Athens, Greece

Dr Björn Hibell, Centralförbundet för alkohol-och narkotikaupplysning (CAN), Stockholm, Sweden

Prof. Dr Henk Garretsen, Faculty of social and behavioural sciences, Tilburg University, Tilburg, Netherlands

Prof. Dr Joris Casselman, Centre for forensic mental health, Catholic University of Leuven, Belgium

Dr Carlo Perucci, Department of epidemiology, Local Health Authority, Rome, Italy

Dr Anne-Marie Sindballe, National board of health, Copenhagen, Denmark

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Dr Jean-Pol Tassin, Inserm U 114 Unit, Neuropharmacology, Research Inserm, Collège de France Paris, France

Dr Christina Poethko-Müller, Federal institute for drugs and medical devices, Bonn, Germany

Dr Wolfgang Werdenich, Special detention centre for the treatment of addicted offenders, Office of Justice, Vienna, Austria

Dr Astrid Skretting, National institute for alcohol and drug research, Oslo, Norway

Representatives of the European Commission, Europol and the European Agency for the Evaluation of Medicinal Products (EMA)

Mr Matthias Haldorsson, European Commission (SANCO DG), Luxembourg

Mr Juan Crespo, European Commission (ENTR DG), Brussels, Belgium

Dr Juhana Idänpään-Heikkilä, Sector for pre-authorisation for the evaluation of medicines for human use, EMA, London, UK

Mr Richard Weijenburg, Europol, the Hague, the Netherlands

Additional experts from the EU Member States

Dr Claude Barjhoux, Centre d'évaluation et d'information sur la pharmacodépendance (CEIP), Grenoble, France

Mr Carlo Bertorello, CNR, National council of research, Pisa, Italy

Dr Wim Best, Inspectorate of health care, public health supervisory service of the Netherlands, the Hague, the Netherlands

Dr Robin Braithwaite, City Hospital NHS Trust, Birmingham, UK

Ms Milagros Diego, Government delegation for the national plan on drugs, Madrid, Spain

Dr Conny Eklund, Medical products agency, Uppsala, Sweden

Dr Fernanda Feijão, Instituto português da droga e da toxicoddependência, Lisbon, Portugal

Prof. Álvaro Lopes, Forensic science laboratory of the criminal police, Lisbon, Portugal

Dr Robert Lousberg, Inspectorate of health care, public health supervisory service of the Netherlands, the Hague, the Netherlands

Dr Heini Kainulainen, National research institute of legal policy, department of criminology, Helsinki, Finland

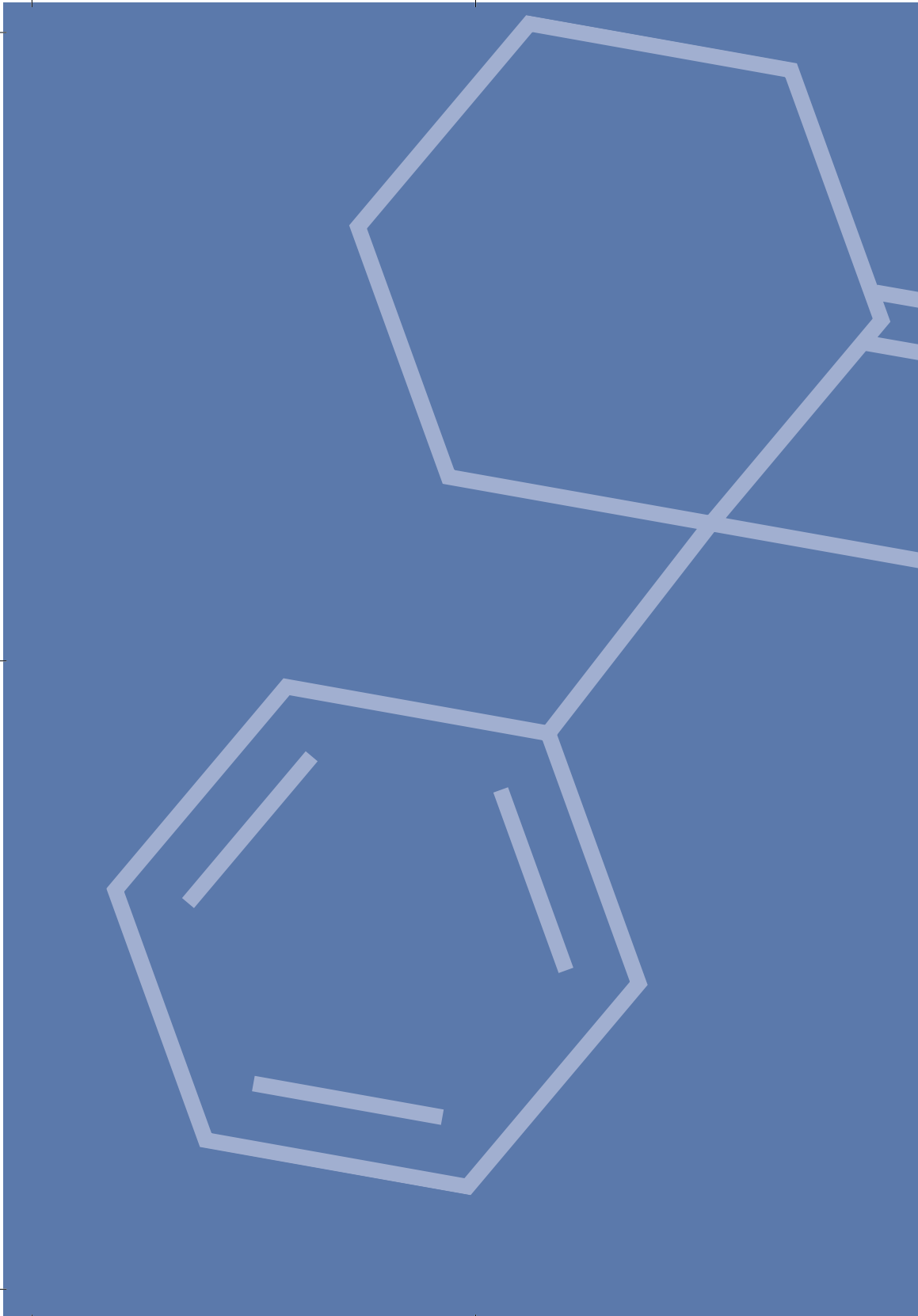
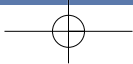
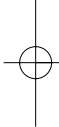
Dr Sean McDermott, Forensic science laboratory, An Garda Síochana, Dublin, Ireland

Dr Henrik Rindom, Psychiatric department, Hvidovre Hospital, Brøndby, Denmark

Prof. Dr Hans Rommelspacher, Free University of Berlin, Berlin, Germany

Dr Hara Spiliopoulou, department of forensic medicine and toxicology, medical school, University of Athens, Athens, Greece

Dr Crista van Haeren, Institut National de Criminologie et Criminalistique, Brussels, Belgium



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