COUNCIL OF THE EUROPEAN UNION

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CORDROGUE 63

NOTE

from :	European Monitoring Centre for Drugs and Drug Addiction
to :	Council and Commission
Subject :	Report on the Risk Assessment of PMMA in the framework of the Joint Action on New Synthetic Drugs

Please find herewith the report on the Risk Assessment of PMMA in the framework of the Joint Action on New Synthetic Drugs that was forwarded to the Council on 6 November 2001.

The report was drawn up by a special meeting in Lisbon on 29 October 2001 and covered by the EMCDDA under the auspices of its Scientific Committee. The report is the second phase provided for in the Joint Action of June 1997 on New Synthetic Drugs.
The third phase foresees that the Council may, on the basis of an initiative to be presented within a month from the date on which the report of the results of the risk assessment is established and acting in accordance with Article K.3 (2) (b) of the Treaty, adopt unanimously a decision defining the new synthetic drug or drugs which will be made subject to necessary measures of control.
If the Commission deems it necessary to propose that a new synthetic drug or drugs be controlled, it is expected to present, within a delay of one month, an explanatory report to the Council.

Report on the Risk Assessment of PMMA in the Framework of the Joint Action on New Synthetic Drugs

On 29 October 2001, a meeting was held 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 to assess the health and social risks of PMMA, especially in association with PMA, as well as the possible consequences of prohibition. This meeting followed from the formal notification of the Swedish Presidency of the Council of the European Union for 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

These documents in conjunction with further information and comments from the expert participants formed the basis of the Risk Assessment which is reported below.

1. 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.

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 commercially available. PMMA and PMA have no therapeutic value.

In general, colour tests are presumptive and need confirmation: limited data indicated that 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 . PMMA gives a positive blue colour of a secondary amine, while PMA does not elicit a colour. Additional complications arise with colour tests on tablets that contain mixtures of different amphetamine analogues.

2. PHARMACEUTICAL DESCRIPTION

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

3. HEALTH RISKS

(Documents I and II)

3.1 Individual Health Risks

(a) Acute Effects

A recent animal study indicates that PMMA induces awakening and stimulant effects.

In discrimination studies, in MDMA ('ecstasy') trained rats PMMA is considered as identical to MDMA. In PMMA trained rats MDMA is considered as identical to PMMA, but this is not the case for amphetamine and the hallucinogen DOM.
Lacking of hallucinogen-like stimulus properties, PMMA may have mostly 'entactogenic' effects, while PMA has a degree of amphetamine-like character.

Pharmacokinetics experiments with five amphetamine-like stimulants revealed a poor penetration of PMA into the brain. Comparisons of the brain levels of these amphetamines suggest hat PMMA crosses the brain barrier even less than PMA.

Neurochemical effects of PMMA have not been investigated in *in vitro* studies. Structure-activity investigations on neurotoxic effects of amphetamine derivatives suggested that PMMA is a serotonin (5-HT) releaser, yielding potent and selective effects on serotonergic neurons. Repeated administration of PMMA (or PMA) in rats produced after four days a brain depletion of serotonergic markers. Recent as well as previous animal experiments in rats and mice produce symptoms considered as 'serotonergic syndrome' but not including all symptoms (e.g., short-term respiratory depression).

The neuronal basis for the hyperactivity and the sympathomimetic stimulation is still unclear. Unlike MDMA, PMA and PMMA do not seem to release dopamine. From its chemical structure, PMMA may probably play a dominant role in the inhibition of monoamineoxidase-A (MAO). *In vitro* experiments demonstrated that PMA is a potent inhibitor of MAO. As it 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 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, the rats present hypertension and long-lasting tachycardia ; these cardiovascular effects are dose-dependent. MAO inhibition may contribute to the long-lasting cardiovascular effects.

The main acute effect for acute toxicity of PMMA in rats is hyperthermia. This effect occurs quickly 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 lethal dose value (LD_{50}, subcutaneous) of PMMA was 80-100mg/kg in rats. The value suggests a narrow margin between the behaviourally active and lethal dose and therefore a high risk for acute toxicity. PMA has a similar toxicity (LD_{50}) than PMMA in mice.

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

(b) Clinical Effects

PMMA without PMA in tablets marketed as 'ecstasy' has been associated with one death in Spain in 1993. Due to the presence of significant concentrations of MDEA and ethanol in the blood sample, the role of PMMA in this death was considered by forensic experts as problematic.

During the recent outbreak of seizures in the European Union of PMMA in combination with PMA, there appeared to be some tablets in which PMMA is the principal substance (e.g., 97 mg in one tablet with 4 mg PMA). In most cases, PMMA was found in combination with PMA and other drugs (e.g., MDA, MDMA, amphetamine, methamphetamine, ephedrine).

PMMA/PMA have been involved in three deaths in the European Union (Denmark) between July and September 2000.

PMA without PMMA has been implicated in a number of deaths in the Member States since June 2000 : one in Austria, two in Germany in 2000 and four in Belgium in 2001. Hyperthermia (up to 41,5-46,1°C) was a recurrent symptom in a number of documented cases on 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 temperature and water deprivation also augmented the hyperthermia. The acute toxicity of PMA and PMMA may be due to the increased extraneuronal serotonin.

Blood concentrations of PMMA in the human cases of fatalities were within the same range as the blood concentrations of PMA or MDMA which are found in the case of deaths.

When monitoring the plasma concentration-time curve (AUC), the findings in rats that PMMA and MDMA maximum effect occurs 15 minutes after their administration, may be an indication in analysing causes of overdose leading to human fatalities. The risk of overdose could be linked to the fact that, after receiving a weak stimulant effect with the same delay as with MDMA, 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 increase toxicity and may present an additional risk factor in the case of overdose.

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

(c) Dependence

PMMA has only been studied in drug discrimination learning by animals. Low doses of PMMA (1.25 mg/kg) have a discriminative stimulus similar to that induced by 'entactogen' substances like MDMA. There have been no systematic studies of PMMA dependence potential in animals or in humans. The lack of dopamine effect 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, on a long-term, fake 'ecstasy' tablets combining PMMA and PMA could replace MDMA on the retail market.

(d) 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 stimulant and to hallucinogenic (LSD) effects. Anecdotal reports from 'ecstasy' users, although not entirely consistent, indicate that it has frequently more unpleasant effects than 'ecstasy'.

3.2 Public Health Risks

(a) Availability and Quality

There appears to be no explicit consumer market in the European Union for either PMA or PMMA. PMMA is sold on the illicit market to substitute for 'ecstasy'. The combination with PMA in tablets sold with an 'ecstasy' type logo does not seems to be the result of an hazard but more probably of a voluntary association of the two compounds whose behavioural effects were described in the existing literature, in order to imitate as much as possible the expected effects of MDMA among users. The large availability of the precursors implicated in the synthesis of both PMMA and PMA may have facilitated this operation.

Since June 2000, four Member States (Austria, Denmark, Germany and Sweden) reported nine large seizures of PMMA together with PMA in tablets consumed as 'ecstasy'. The Netherlands reported three large seizures of tablets containing PMA with MDMA or MDA and two seizures of tablets containing PMA. The significant amount 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 UK 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 'Trefoil 4 Leaves' logo has been found. Other tablets containing PMA (without PMMA) have carried 'Mitsubishi', 'Elephant', 'Nike', 'Superman', and 'xTc' logos.

PMMA has always[1] been found in combination with PMA in tablets sold as 'ecstasy'. Most PMMA/PMA tablets contained a mixture with amphetamine, methamphetamine or ephedrine. On the basis of the available information, tablets contain between 20 and 97 mg PMMA.

(b) Knowledge, Perceptions and Availability of Information

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, TV, newspapers and 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 evidence on the knowledge or the perceptions of PMMA alone or when combined with PMA among users as there is no market for PMMA/PMA.

[1] With the exception of Spain, where three seizures took place between August and October 2000 of a small number of tablets containing PMMA, without specifying any other drug contents.

(c) Prevalence and Patterns of Use

Prevalence of (inadvertent) use of PMMA depends on the extent to which it is being sold as 'ecstasy', which is currently the case. It 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 due to the search by users of similar effects to MDMA. In that regard, the combination of PMA with PMMA represents a major risk.

(d) Characteristics and Behaviours of Users

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

Special concerns relates to lack of knowledge about both 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 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 risk. 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.

(e) Indicators of Health Consequences

In Spain, there has been one death case associated with PMMA alone in 1993, and one death case with PMA in 1995. Since 1995, PMA has been implicated in at least eight deaths in Australia and ten in the USA.

Since July 2000, there have been three deaths recorded as linked with PMMA/PMA in Denmark and seven other deaths have been recorded as linked to PMA in three other Member States: one in Austria, 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 death 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 investigations for PMA may have been prompted by heightened awareness of the potential role of PMA in 'ecstasy' intoxication.

(f) 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.

4. SOCIAL RISKS: Sociological/criminological aspects

(Documents III and IV)

4.1 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.

4.1.1 Social Consequences

There is no evidence specifically 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 the interest in health issues and avoiding harm from new synthetic drugs is evident.

4.1.2 Consequences for the Social Behaviour of the User

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

4.1.3 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.

4.2 Criminological Aspects

Distribution of PMA has 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 has taken place in four Member States: Austria, Denmark, Germany and Sweden.

In 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 amount of seized PMA and PMMA/PMA tablets in the Member States in 2000 is relatively small when compared to overall 'ecstasy' seizures in the European Union (17,426,531 tablets in 2000). Large-scale production of PMA or PMMA does not occur in any Member State.

Three Member States, Austria, Denmark 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 BKA and the fact that the Polish authorities seized two illicit laboratories for the production of PMA and PMMA, leads to the conclusion that PMMA/PMA tablets seized in the Member States, Canada and the United States, 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 in 2000.

5. POSSIBLE CONSEQUENCES OF PROHIBITION

5.1 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 United Kingdom. In Norway, PMMA is also controlled. Steps are being taken in France to schedule PMMA under its national drugs legislation. Recently, an assessment on PMMA/PMA has 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 United Nations Convention on Psychotropic Substances since 1986.

5.2 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 as less serious, there was strong support of the meeting that prohibition is the most appropriate measure of control. Another point of view expressed at the meeting was that PMMA can not 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 reduction 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.

6. CONCLUSIONS

The Scientific Committee of the EMCDDA extended with experts from the Member States and representatives of the Commission, Europol and EMEA have considered the health and social risks as well as the possible consequences of prohibition of para-methoxymethylamphetamine (PMMA) as such and when associated in 'ecstasy'-like tablets in combination with the controlled drug para-methoxyamphetamine (PMA) and in accordance with Article 4 of the Joint Action submit the following conclusions:

6.1 PMMA has no therapeutic value.

6. 2 The scientific evidence submitted to the meeting shows that PMMA is a psychoactive agent which seems to release serotonin and may inhibit monoamineoxidase-A activity. It has been associated in combination with PMA with three deaths within the EU. The reported adverse events are noteworthy in that they have occurred 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 of the lack of other expected 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 of organised crime in the trafficking of PMMA. PMMA is almost exclusively sold in combination with PMA and consumed as 'ecstasy'. Anecdotal reports suggest that PMMA/PMA tablets may be less attractive than MDMA to users because of its unpleasant effects.

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 the gaps in knowledge. Further studies should be conducted to establish the exact role of PMMA in those toxic effects.

6.3 Arising from 6.1 and 6.2 and because PMMA is an amphetamine analogue very close to PMA and 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 recommends that a decision to place PMMA under control should not inhibit the gathering of information about drugs on the market and the dissemination of accurate information on PMMA and PMMA/PMA to users and to relevant professionals. The risk of overdosing should be highlighted, as should the risks of consuming it with alcohol, MDMA, amphetamines, and ephedrine products.

6.4 The major chemical precursors of PMMA are commercially available. The meeting recommends that the Drug Precursors Committee set up under Article 10 of Regulation 3677/90 and Directive 92/109/EEC be invited to closely examine the situation of the specific precursor chemicals which have been found in the manufacture of PMMA and which are not yet subject to any measure of surveillance.

6.5 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 reference standard material and associated analytical data to forensic and toxicology laboratories within the European Union. The meeting further recommends that PMMA be included within the UNDCP proficiency testing programme.

Lisbon, 29 October 2001