

# **para-Methoxymethylamphetamine (PMMA)**

## **Critical Review Report**

### **Agenda item 5.6**

**Expert Committee on Drug Dependence**

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**World Health  
Organization**



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## Acknowledgements

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## Summary

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PMMA (para-methoxymethylamphetamine) is a synthetic phenethylamine drug structurally related to methamphetamine and PMA (para-methoxyamphetamine), which are both listed in the 1971 United Nations Convention on Psychotropic Substances. PMA is also a metabolite of PMMA. PMMA has been available since the 1980s initially in powder form but subsequently as tablets invariably purported to be “Ecstasy”. Animal studies have shown that PMMA is more associated with the serotonergic system than dopaminergic or noradrenergic systems. Based on PMA studies, PMMA is also speculated to be an inhibitor of monoamine oxidase type A. In animal discrimination studies, PMMA lacks amphetamine-like (stimulant) and DOM-like (hallucinogen) effects but generalised to MDMA. Over the last three decades but especially within the last 5 years, PMMA has been associated with 31 non-fatal intoxications and 131 deaths in three continents (mainly Europe). Symptoms in users have included tachycardia, hyperthermia, convulsions, breathing problems and cardiac arrest and whilst other drugs (especially MDMA) were involved in the majority of cases, some only involved PMMA. The slow onset of PMMA effects supported by *in vivo* animal studies has resulted in some users re-dosing, increasing the likelihood of toxicity. Extrapolated animal studies have indicated an abuse potential for PMMA and possible low potential for dependence but no human data are available.

**1. Substance identification****A. International Nonproprietary Name (INN)**

Not applicable

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

Hydrochloride salt: 3398-68-3

**C. Other Names**

Para-methoxymethylamphetamine  
Para-methoxymethamphetamine  
4-methoxymethylamphetamine  
Paramethoxy-N-methyl-amphetamine  
N-methyl-1-4-(methoxyphenyl)-2-aminopropane  
4-methoxy-N-methyl-amphetamine  
1-(4-methoxyphenyl)-2-methylaminopropane  
Benzeneethanamine, 4-methoxy-N, $\alpha$ -dimethyl-  
Phenethylamine, N, $\alpha$ -dimethyl-p-methoxy-  
p-Methoxy-N, $\alpha$ -dimethylphenethylamine  
2-methylamino-1-(p-methoxyphenyl)propane  
4-MMA  
( $\alpha$ S)-N, $\alpha$ -Dimethyl-4-methoxy-benzeneethanamine

**D. Trade Names**

None

**E. Street Names**

PMMA is predominantly sold as “Ecstasy” in tablet form, although it was originally sold as a powder.<sup>1</sup> Tablets containing PMMA with various logos have been encountered but more recently a “Superman” logo has predominated again.<sup>1,2</sup> PMMA (and PMA) have sometimes been associated with the colloquial names “Dr Death”, “Death” and “Killer”.<sup>3,4</sup>

**F. Physical properties**

The hydrochloride salt is a white powder with a melting point of 177-178°C.

**G. WHO Review History**

PMMA has not been previously reviewed by WHO.

## 2. Chemistry

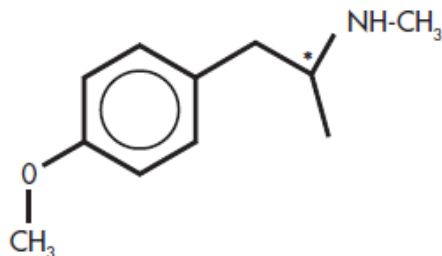
### A. Chemical Name

**IUPAC Name:** [1-(4-methoxyphenyl)propane-2-yl](methyl)azane]]

**CA Index Name:** Not applicable

### B. Chemical Structure

**Free base:**



**Molecular Formula:** C<sub>11</sub>H<sub>17</sub>NO

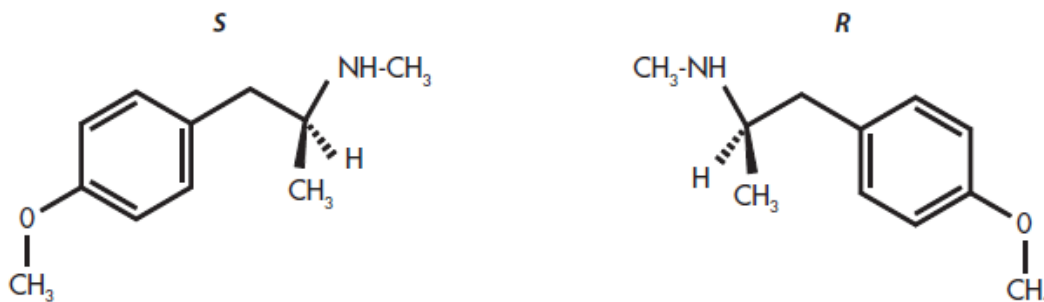
**Molecular Weight:** Free base = 179.259

**Melting point:** 177–178°C

**Boiling point:** Not known

### C. Stereoisomers

PMMA has a chiral centre (\* shown above) resulting in two optical isomers; R- and S+.



### D. Synthesis

#### Methods of manufacturing:

The 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 chloroformiate, triethylamine, carbamate, formamide and lithium aluminium hydride. The synthesis of PMMA has been described by Shulgin and Shulgin.<sup>5</sup> The possible synthetic routes (i.e. Leuckart method) used by illicit



laboratories have been discussed based on PMA<sup>6</sup> and have been studied specifically for PMMA.<sup>7</sup>

**E. Chemical description.**

PMMA is a substituted phenethylamine being a methoxy-derivative of methamphetamine. Methamphetamine is a Schedule II substance under the 1971 United Nations Convention on Psychotropic Substances. PMMA is also related to para-methoxyamphetamine (PMA) which is a Schedule I substance under the 1971 United Nations Convention on Psychotropic Substances.

**F. Chemical properties**

See Section B and G. PMMA is a white powder. PMMA is found in solid form in user products. There are no solubility data.

**G. Chemical identification**

PMMA gives the following results using field reagent tests; Marquis: No colour. Mecke: Pale olive green. Secondary amine: Blue. Frohde: Pale green. Mandelin: Rust. Liebermann: Purple-brown.<sup>8,9</sup>

The ultraviolet, proton magnetic-resonance, and infrared spectrum of PMMA has been published in papers by Bailey *et al.*, Clark and Dal Cason.<sup>8-12</sup>

PMMA gives a positive finding with immunoassay testing for amphetamines which is commonly used in preliminary laboratory or point-of-care testing but requires confirmation invariably using chromatographic techniques.<sup>13</sup> Such techniques including GC-MS analysis have been described<sup>14-17</sup> as well as LC-MS.<sup>18-20</sup>

**3. Ease of convertibility into controlled substances**

No information available (especially in relation to possible conversion to para-methoxyamphetamine or methamphetamine).

**4. General pharmacology**

**A. Pharmacodynamics**

Neuropharmacology

There is no information regarding the *in vitro* activity of PMMA, however studies of PMA may be representative. In mouse brain homogenate, PMA was found to be over 20 times more potent than (+)amphetamine as an inhibitor of 5-HT oxidation by MAO (monoamine oxidase), exhibiting a  $K_i$  value of 0.22  $\mu\text{M}$ , with (+)amphetamine 6  $\mu\text{M}$ , o-methoxyamphetamine 9  $\mu\text{M}$  and m-methoxyamphetamine 23  $\mu\text{M}$ . PMA is highly selective towards A-type MAO and possesses only weak activity against B-type enzyme.<sup>21</sup> 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  $\mu\text{M}$  (competitive initial non-covalent interaction) and of moclobemide is 200  $\mu\text{M}$ .<sup>22</sup> Others reported a  $K_i$ -value of 0.0063  $\mu\text{M}$  for clorgyline using crude mitochondrial fraction from rat brain as the source of MAO-A.<sup>23</sup> The high inhibitory potency of PMA is an important observation with respect to the toxic actions of PMA and probably of PMMA, as well as being a poor substrate for MAO. Therefore, the inactivation of phenylpropylamines such as PMMA 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 that the difference in potency is more than 40-fold compared with the ortho- and meta-substituted compounds.

Whilst there are no extensive or specific studies for PMMA regarding monoaminergic systems, the findings of MDMA may be relevant. 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  $\mu\text{M}$ ).<sup>24</sup> 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.<sup>25</sup>

#### 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.<sup>26</sup> 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.<sup>27</sup> Thus, both types of neurones could 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.<sup>28-29</sup> PMMA did not produce significant locomotor stimulation at doses up to 30 mg/kg in mice. At doses greater than its  $LD_{50}$  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.<sup>30</sup> 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. Also, MDMA seems to possess greater central stimulant character than PMMA whereby it produces a hyperlocomotor effect in rodents that is essentially absent following administration of PMMA.<sup>30</sup>

The actions of PMMA observed in animals and human users 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 in knock-out mouse models. The activation of 5-HT<sub>1B</sub> receptors, which probably mediate the actions of low doses of PMMA, causes hypophagia, hypothermia, penile erection, increased release of corticosterone and prolactin. 5-HT<sub>1B</sub> receptor agonists have an anti-aggressive action and induce myoclonic jerks. The activation of 5-HT<sub>2A</sub> 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-HT<sub>1R</sub> agonists) hallucinations, and elevation of cortisol, ACTH, renin, and prolactin. The activation of 5-HT<sub>2C</sub> 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.

#### Cardiovascular effects

PMMA produces cardiovascular and other sympathomimetic effects by what is believed to be an indirect mechanism.<sup>31</sup> A 0.2 mg/kg dose showed prolonged cardiovascular effects in the dog.<sup>32</sup> 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.<sup>33</sup> 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 blood pressure (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.

#### Behavioural studies

PMMA has 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.<sup>30</sup> However, it has been shown that stimulus generalisations occur in animals trained to discriminate MDMA from vehicle.<sup>34</sup> Specifically, six rats were trained to discriminate 1.25 mg/kg of PMMA (ED<sub>50</sub>=0.44 mg/kg) from saline vehicle. The PMMA stimulus failed to generalise to (+)amphetamine or the hallucinogen DOM. Stimulus generalisation occurred to (±) MDMA (ED<sub>50</sub>=1.32 mg/kg) and S(+)-MDMA (ED<sub>50</sub>=0.48 mg/kg). Partial generalisation occurred with R(-)-MDMA, PMA, 3,4 DMA and fenfluramine. The PMMA stimulus also generalised to PMEA (ED<sub>50</sub>=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.<sup>34</sup> A later study also by Glennon *et al.* demonstrated that (unlike MDMA) PMMA only partially substituted for cocaine, with cocaine producing a maximum of 46% PMMA-appropriate responding (at 5.0 and 7.5 mg/kg).<sup>35</sup> Higher cocaine doses (i.e., 10 and 15 mg/kg) failed to elicit greater PMMA-appropriate responding, or disrupted the animals'

lever pressing behaviour. Except at the lowest dose evaluated, one animal failed to respond following administration of each of the higher cocaine doses.

Researchers have investigated whether the stimulant effects in drug discrimination experiments are stereoselective.<sup>36</sup> S(+)-PMMA (ED<sub>50</sub>=0.32 mg/kg) was found to be at least as potent as racemic PMMA (ED<sub>50</sub>=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 stimulant component of action associated with MDMA. These findings suggest that the S(+) enantiomer of PMMA is the active compound.

#### Human data

There are no reported human clinical trials with PMMA. However, a study by Brunt *et al.* of “Ecstasy” users analytically confirmed 70 individuals who had taken PMMA and MDMA together resulting in adverse effects (especially hyperthermic seizure and palpitations along with agitation, nausea and in some cases, hallucinations).<sup>37</sup> Probability calculations indicated a very high likelihood of adverse effects when the two drugs were taken in combination, more than compared to MDMA alone and other MDMA drug combinations. No individuals had only ingested PMMA.

#### **B. Routes of administration and dosage**

PMMA was originally used as a powder (with doses typically >100 mg).<sup>1</sup> However, the form in which PMMA is commonly encountered now is as tablets. Tablets containing PMMA have been seized in Europe, Asia and the Americas.<sup>1,2,38</sup> They are predominantly tablets sold as “Ecstasy” and are marked with a number of different logos such as ‘E’, ‘Mitsubishi’ or ‘Jumbo’. Whilst also seen in the early 2000s, tablets containing PMMA with a ‘Superman’ logo have been associated with a number of deaths in the last few years (see Section 6).

PMMA is invariably always found in combination with PMA in tablets sold as “Ecstasy”, sometimes along with amphetamine, methamphetamine or ephedrine. In the 2003 the EMCDDA reported that tablets contain between 20 and 97 mg PMMA.<sup>1</sup>

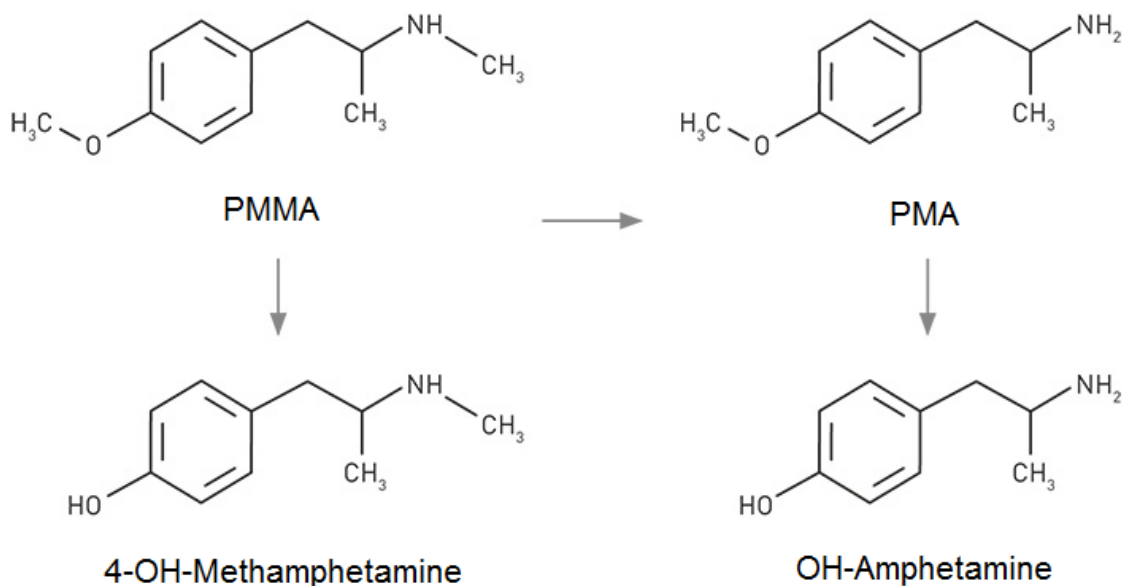
Due to availability in tablet form, the most common route of administration of PMMA is oral. Internet reports by users suggest doses between ~50 mg and ~250 mg.<sup>3</sup>

#### **C. Pharmacokinetics**

Published pharmacokinetic data for PMMA in animals and humans are limited. However, rat studies by Rohanova and Balikova involved a bolus subcutaneous dose of 40 mg/kg of PMMA.<sup>39</sup> The maximum plasma PMMA concentration of 4014±1122 ng/mL was reached 30 minutes after dosing, whereas the appearance of metabolites was delayed. Approximate half-life of 1.0 hours, volume of distribution of 6.4L/kg and plasma clearance of 4.4L/h were found. PMMA tissue concentration exceeded plasma and the highest one was found in the lungs (C<sub>max</sub>) 42,988±10,223 ng/g). Penetration of PMMA through the blood/brain barrier was more efficient compared to PMA and its hydroxylated metabolites. The maximum brain/plasma ratio value of PMMA (15.8) and PMA (11.8) was reached after 8 hours of observation.

Further rat studies by Páleníček *et al.* found that following the administration of PMMA at 5 mg/kg and 20 mg/kg, PMMA concentrations in serum achieved a maximum after 30 min for both doses with a rapid decline.<sup>40</sup> Although some traces could be detected for the higher dose after 4 hours, none could be detected after 8 hours. For the higher dose (20 mg/kg) there was a clear time delay of the concentration maxima attained in brain (60 minutes) compared to serum (30 minutes). The PMMA brain levels significantly exceeded those in serum which indicated the high degree of drug incorporation into the brain. The authors speculated that the temporal profile of PMMA in the brain may be associated with the time course of some of its psychotropic effects.

Staack *et al.* indicated that in rats PMMA was extensively metabolized mainly by O-demethylation to active pholedrine (para-hydroxymethamphetamine, OH-MA) and to a minor extent to PMA, 1-hydroxypholedrine diastereomers (one being oxilofrine), 4'-hydroxy-3'-methoxymethamphetamine and 4'-hydroxy-3'-methoxyamphetamine.<sup>15</sup> Subsequent studies by Staack *et al.* using baculovirus-infected insect cell microsomes, pooled human liver microsomes (pHLMs), and CYP2D6 poor-metabolizer genotype human liver microsomes (PM HLMs) found that only CYP2D6 catalyzed the O-demethylation of PMMA (to OH-MA).<sup>19</sup> The apparent  $K_m$  and  $V_{max}$  values in baculovirus-infected insect cell microsomes were 4.6 +/- 1.0  $\mu$ M and 92.0 +/- 3.7 pmol/ min/pmol P450, respectively, and 42.0 +/- 4.0  $\mu$ M and 412.5 +/- 10.8 pmol/min/mg protein in pHLMs. Inhibition studies with 1  $\mu$ M quinidine showed significant inhibition of the metabolite formation (67.2 +/- 0.6%;  $p < 0.0001$ ), and comparison of the metabolite formation between pHLMs and PM HLMs revealed significantly lower metabolite formation in the incubations with PM HLMs (87.3 +/- 1.1%;  $p < 0.0001$ ). It was concluded that CYP2D6 is the major P450 involved in O-demethylation of PMMA. This work was recently confirmed by Vevelstad *et al.* using *in vitro* human liver microsomes and showed that PMMA metabolises to 4-OH-MA (mainly), PMA, 4-hydroxyamphetamine and dihydroxymethamphetamine (di-OH-MA).<sup>41</sup> It was also shown that the CYP2D6 genotype had a major impact on the metabolism of PMMA and that with the exception of PMA, the other minor PMMA metabolites can also be formed as a result of MDMA and methamphetamine metabolism.



Repeated intakes of PMMA 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 which is shared by PMMA.<sup>42</sup> The relevance of the inactive CYP2D6 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.<sup>43</sup> 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. Specifically, the use of PMMA may cause metabolic interactions with other drugs that are CYP2D6 substrates and the potential for polymorphic oxidation via CYP2D6 may be a source of inter-individual variation in its 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),  $\beta$ -adrenoceptor blockers (e.g. metoprolol), deprenyl (N-propargyl methamphetamine), inhibitors of MAO-B; and methoxymorphinans.

## 5. Toxicology

Clinical information has been recorded in some instances of human use. In a cluster of deaths occurring in Norway, death was witnessed in 4 cases, with symptoms of acute respiratory distress, hyperthermia, cardiac arrest, convulsions, sudden collapse and/or multiple organ failure.<sup>4</sup> Importantly, 3 fatalities were attributed to PMMA only. This was supported by Nichol *et al.*<sup>44</sup> where clinical features were described to be consistent with "serotonin syndrome" where symptoms can include tachycardia, hypertension, hyperthermia, muscle rigidity and convulsions.<sup>45-47</sup> An apparent slow onset of PMMA effects described by users was supported by the *in vivo* animal studies of Páleníček *et al.*<sup>40</sup>

showing a delay in maximum brain concentration compared to the serum and presents more chance that users will re-dose, increasingly the likelihood of toxicity.

#### Animal studies

In rodent studies of aggregation (the presence of other mice to reflect social stress), PMMA did not show any significant difference in acute toxicity in mice under isolated (24 h LD<sub>50</sub> = 63 mg/kg) or aggregated (24 h LD<sub>50</sub> = 53 mg/kg) conditions, suggesting a lack of amphetamine-like toxicity.<sup>30</sup> Although not fully characterised, the LD<sub>50</sub> of PMMA is in the range of 80–100 mg/kg in rats. 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.<sup>26</sup>

Steele *et al.* 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.<sup>26</sup> 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 at 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.

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 analogue.<sup>26</sup> The number of 5-HT transporters (<sup>3</sup>H]paroxetine binding sites) decreased in rat cortex with 80 mg/kg PMMA, suggesting damage or loss of 5-HT terminals ( $p < 0.05$ ).<sup>26</sup> There is debate, however, as to whether neurotoxicity findings in animals can be extrapolated to humans.

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

Human data

There have been no human clinical trials of PMMA. As stated elsewhere, a study by Brunt *et al.* of “Ecstasy” users who had used PMMA and MDMA in combination described adverse effects such as hyperthermic seizure and palpitations (in particular) along with agitation, nausea and in some cases, hallucinations.<sup>37</sup> Probability calculations indicated a very high likelihood of adverse effects when the two drugs were taken in combination, more than compared to MDMA alone and other MDMA drug combinations.

In a self-dosing report of PMMA by Shulgin<sup>5</sup> he took 110 mg and stated the following: “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”. With regard cardiovascular effects, Shulgin stated in the same report that one hour after taking 110 mg PMMA orally his pulse was over 100 beats/minute and that all indications of the cardiovascular effects of MDMA were there. Previously, in 1978, Shulgin had stated that the somatic effects can persist for over two hours, together with BP elevation.<sup>48</sup> Paraesthesia was still observed four hours after administration. 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.

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 PMMA. The user expecting these effects may assume that the dose is too low and take more tablets. This is also coupled with the work of Páleníček *et al.* showing that in animals there is a delay in the maximal concentration in brain compared to serum.<sup>40</sup> The apparent delayed effect and subsequent re-dosing has been a defining feature in some of the deaths involving PMMA. 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 and animal experiments suggest that PMMA is less toxic than PMA. The reason for both observations might be that PMMA penetrates the blood-brain barrier less easily than PMA. The acute toxicity of PMMA (and PMA) is likely 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.

Internet user reports involving doses between ~50 mg and ~250 mg describe desired effects of stimulation, lock jaw and relaxation with euphoria at higher doses purportedly similar but less than that of MDMA.<sup>1,49</sup> Conversely, temperature control problems, eye rolling and audiostimulation were described. One subject observed a steep dose response curve for PMMA. 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, with head and stomach pain. 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 PMMA was 'not psychedelic' but another subject taking 215 mg stated that it was.

More recent user reports have mentioned hyperthermia and re-dosing in particular.<sup>3</sup>

In the fatalities reported by Nicol *et al.*, 17 of the 27 individuals died in hospital and clinical symptoms were noted.<sup>44</sup> Heart rate 160 (86–201) beats/min, blood pressure 89/43 (69/30–162/83) mm Hg, respiratory rate 40 (26–48) breaths/min, oxygen saturation 81% (68%–100%) and temperature 39.4°C (34–43.8°C). Sixteen of the 17 people presented with clinical features consistent with serotonin syndrome. End-organ dysfunction included hepatic (30%) and acute kidney injury (85%), rhabdomyolysis (54%), coagulopathy (61%) and cardiac ischemia (15%). Other drugs identified on toxicological analysis were MDMA (n=27), cocaine or its metabolite benzoylecgonine (n=14) and methamphetamine (n=12).

In 8 other fatalities reported by Chen *et al.* where ante-mortem neurobehavioral manifestations were recorded following PMMA use, there were two different ante-mortem presentations.<sup>50</sup> The first group of patients showed delirium, hypertalkativity and incoherence speech followed by convulsions and death. The patients did not exhibit the typical hyperdopaminergic movement disorder. The second group of patients gradually fell asleep and then suffered respiratory or cardiovascular collapse. The heart blood PMMA concentration was higher in the second group than in the first group of patients.

## 6. Adverse reactions in humans

There appear to have been clusters of non-fatal cases and fatalities involving PMMA during the last 22 years. Distinct clusters have occurred in each decade; 1990s, 2000s and 2010s, with the first published death occurring in Spain in 1993 at a disco and also involved MDEA, MDA and ethanol.<sup>51</sup> Specific clusters include a 6 month period in Norway (July 2010-January 2011)<sup>4</sup> and one week (December 2014-January 2015) in Sweden.<sup>52</sup>

### Non-fatal cases

A total of 31 analytically confirmed cases have been reported within Europe and Israel.<sup>2,4,53</sup> In 22 Norwegian cases in 2010/11 reported by Vevelstad *et al.* the median age was 27 years (range 20-47) with 86% of patients being male.<sup>4</sup> The median PMMA concentration was 0.07 mg/L (range 0.01-0.65 mg/L). Poly-drug use was frequent and although PMA was detected the authors purported that due to the comparatively lower concentration, this may be due to its presence as a metabolite. In 5 cases in Israel, all patients were males with an average age of 32 years.<sup>53</sup> Four of the patients had taken other drugs including cocaine, cannabis and cathinones.

### Fatal cases

A total of 131 analytically confirmed deaths where PMMA was detected (in either blood and/or urine) have been reported in Europe (69 deaths), Israel (27 deaths), Canada (27 deaths) and Taiwan (8 deaths).<sup>2,4,20,44,50-57</sup> The deaths occurred across the following decades; 1990s (1 death), 2000s (40 deaths) and 2010s (90 deaths).

Some specific published information is available on a selection of these cases;

The death reported by Lora-Tamayo *et al.* that occurred in Spain, 1993, involved a 17 year old male who became ill at a disco and died a few minutes later.<sup>51</sup> A post-mortem blood PMMA concentration of 1.51 mg/L was detected along with MDEA (2.00 mg/L), MDA (0.30 mg/L) and ethanol (20 mg/dL).

For the 3 cases reported by Johansen *et al.* in Denmark, case 1 involved a 20 year old male admitted to hospital with hallucinations having been drinking and taking 4 “Ecstasy” tablets with a ‘Mitsubishi’ logo.<sup>56</sup> He developed an arrhythmia and went into cardiac arrest. His rectal temperature was 42°C. Post-mortem blood found PMMA (3.3 mg/kg = approximately mg/L), PMA (3.4 mg/kg), MDMA (1.6 mg/kg), tetra-hydrocannabinol (THC) and ethanol (0.07%). The cause of death was cited as MDMA, PMMA/PMA overdose. Case 2 also involved a 20 year old male how died in hospital 4 days after ingestion having taken “Ecstasy” tablets. He had developed paranoia and upon presentation was in coma with spasms. A body temperature of 40.2°C was recorded. He died following multi-organ failure. PMMA and PMA were detected in admission serum and post-mortem liver at observed high concentrations (not quantified). The cause of death was cited as multi-organ failure due to PMMA/PMA. Case 3 also involved a 20 year old male who had taken an “Ecstasy” tablet followed by two additional tablets. He began sweating intensively and became hyperactive with excessive walking. Friends tried to make him drink water, but he aggressively refused. Approximately two-and-a-half hours later, he became lifeless. At the hospital, resuscitation was tried unsuccessfully. His rectal temperature was 42.8°C. Post-mortem blood found PMMA (0.68 mg/kg), PMA (0.78 mg/kg), MDMA (0.08 mg/kg), benzoylecgonine (0.08 mg/kg) and ethanol (0.03%). The cause of death was cited as PMMA/PMA overdose.

The reported death of a 22-year-old German male occurred after the ingestion of “Ecstasy” pills containing PMMA and PMA.<sup>55</sup> The PMMA concentration in femoral blood was 0.85 mg/L with PMA (0.61 mg/L). In addition, amphetamine (0.21 mg/L), benzoylecgonine (<0.01 mg/L) and ethanol were found in the blood.

In 12 Norwegian cases in 2010/11 reported by Vevelstad *et al.* the median age was 30 years (range 15-50) with 67% of decedents being male.<sup>4</sup> Three fatalities were attributed to PMMA only, six to PMMA and other psychostimulant drugs, and three to PMMA and CNS depressant drugs, with median PMMA concentrations of 3.05 mg/L (range 1.58-3.30 mg/L), 2.56 mg/L (1.52-3.23 mg/L) and 0.52 mg/L (0.17-1.24), respectively.

In Taiwan, Lin *et al.* and Chen reported 8 PMMA-related fatalities in 2006 involving 7 males and 1 female with an average age of 19 years (range 14-25 years).<sup>50,54</sup> The mean post-mortem heart blood concentration of PMMA was 4.31 mg/L (range 1.21-15.82 mg/L). The mean post-mortem heart blood concentration of PMA was 0.21 mg/L (range 0.08-0.49 mg/L) Other drugs, including MDMA, MDA, ketamine, hydroxymidazolam, methamphetamine and pentobarbital were also found in these cases. Forensic autopsy showed variable findings, ranging from no remarkable change to significant pathological damage similar to serotonin syndrome.<sup>50</sup>

In 24 fatalities reported by Lurie *et al.* in Israel where PMMA and PMA was detected, the average age was 27 years and 79.2% were male.<sup>53</sup> Mean post-mortem whole blood PMMA

concentrations were  $0.35\pm 0.24$  mg/L with PMA concentrations of  $2.72\pm 1.67$  mg/L. Additional drugs were detected in 17 cases (70.8%) and included MDMA, MDA, cocaine, cannabis, cathinones, ephedrine/pseudoephedrine, opiates and ethanol.

In 7 fatalities that occurred over a single week in Sweden (25<sup>th</sup> December 2014-1<sup>st</sup> January 2015), 5 were male, 2 were female with 6 of the individuals presenting with severe lung oedema.<sup>52</sup> 3 of the decedents were witnessed with signs of breathing difficulties prior to collapse and seizure followed by cardiac arrest. The concentrations of PMMA in the post-mortem femoral blood were 3.3-7.1  $\mu\text{g/g}$  (approximately equivalent to mg/L) but one case with a low concentration of 0.03  $\mu\text{g/g}$  involved a long survival period. Other drugs of abuse were detected in all cases including MDMA, amphetamine, cocaine and THC. Whilst PMA was also detected, the concentrations were 6-10% that of PMMA and were thought to be from metabolism. Media reports linked the cases to pills with a ‘Superman’ logo.

A retrospective study by Nicol *et al.* identified 27 deaths involving PMMA between June 2011 and April 2012.<sup>44</sup> 22 were male (81%) and the median age was 24 years old (range 14–52 years) with 10 of the individuals being pronounced dead at the scene and 17 died in hospital. The majority of cases described suspected “Ecstasy”, MDMA or cocaine use. Where PMMA was measured, a median ante-mortem blood concentration of 1.43 mg/L was found (range 0.11–3.27 mg/L). Post-mortem inferior vena cava and central blood median concentration was 2.84 mg/L (range 0.14–4.88 mg/L). Post-mortem femoral and iliac median blood concentration of 4.41 mg/L (range 2.17–15.7 mg/L) was found.

In the UK, 6 published<sup>20</sup> and 5 unpublished findings by Elliott<sup>57</sup> describe 11 deaths involving PMMA that occurred between 2011 and 2015 and are shown in the Annex 1, Table 1. The majority (9) were male with 2 female decedents. Post-mortem blood PMMA concentrations between 1.6-6.4 mg/L (median 2.9 mg/L) were found, where measured. Other drugs at low levels were detected in all cases (especially MDMA and/or amphetamine). In cases where symptoms were observed, these included breathing difficulties, sweating, shaking and high body temperature.

## 7. Dependence potential

As described elsewhere, 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 could indicate a low dependence potential because of the central reinforcing role of dopamine release but no human data have been published to confirm this.

## 8. Abuse potential

As stated above and found by Glennon *et al.* in drug discrimination animal studies, PMMA generalised to MDMA and was approximately three times more potent than MDMA.<sup>34,35</sup>

Whilst PMMA lacks amphetamine-like (stimulant) and DOM-like (hallucinogen) effects, its similarity to MDMA provides some evidence for abuse potential.<sup>30</sup>

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

PMMA was apparently first mentioned in a patent in Germany by Hildebrandt in 1938 but did not result in pharmaceutical production.<sup>58</sup> It seems that there is no relevant therapeutic use for PMMA. Methoxyphenamine (also known as orthoxine) which is a positional analog of PMMA, is used as an adrenergic bronchodilator. It has been used in the prevention of acute asthma attacks in doses up to 200 mg.<sup>5,59</sup> This compound has been controlled in the UK as a prescription medicine and is no longer available as such on the UK market. PMMA is a synthetic precursor of the sympathomimetic agent, pholedrine ('Veritol').<sup>31</sup>

There are currently no other indications that PMMA may be used for legitimate purposes (below). There are no known uses of PMMA as a component in industrial, cosmetic or agricultural products. There is no information that PMMA is currently used in the manufacture of a medicinal product. There is no marketing authorisation (existing, ongoing or suspended) for PMMA.

## **10. Listing on the WHO Model List of Essential Medicines**

PMMA is not listed on the WHO Model List of Essential Medicines.

## **11. Marketing authorizations (as a medicinal product)**

PMMA has never been marketed as a medicine.

## **12. Industrial use**

PMMA has no industrial use.

## **13. Non-medical use, abuse and dependence**

Although PMA use and abuse was first noted in the 1970s, it appears PMMA use and abuse was first noted in the late 1980s, associated with MDMA "Ecstasy" culture. Use and abuse has subsequently been reported worldwide but particularly in Europe as well as Asia and Canada, often in sporadic clusters within weeks or months.

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

From its initial abuse, PMMA has been associated with "Ecstasy" tablets seemingly as a substitute for MDMA although there is little information as to whether PMMA was specifically sought by some users. Where information was available with regards to the reported cases of adverse events, it was reported that the users did not appear to intentionally purchase PMMA on the street market but rather "Ecstasy" tablets or powders. However, some Internet forum users described the specific ingestion of PMMA as part of consumption experiments/experiences.

Instances of misuse, abuse and dependence would be limited to individual users rather than the general population. The mode of use may involve the combinational use (intentionally

or unintentionally) of other drugs. This was particularly evident in the fatalities where various drugs with the potential for toxic interactions (e.g. cathinones, phenethylamines, etc) were also involved and PMMA was cited as being contributory to death. However, in some deaths only PMMA was detected with no other drugs.

There are no specific prevalence data on the overall use of PMMA but available evidence does not suggest very wide use of the substance. However, the occurrence of clusters of adverse events indicates discrete time periods of use inadvertent or otherwise likely to be associated with a localized source of PMMA being distributed as “Ecstasy” or related products, sometimes with specific names or logos.

**15. Licit production, consumption and international trade**

Not applicable.

**16. Illicit manufacture and traffic and related information**

No specific data.

**17. Current international controls and their impact**

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

**18. Current and past national controls**

PMMA is controlled in European Union Member States following a decision of the Council of the European Union in 2002.

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

None.

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## Annex 1: Table 1 UK deaths (n=11) in which PMMA has been detected.<sup>20,57</sup>

Table Key: M: male; F: female; Blood<sup>f</sup>: femoral blood sample; Blood<sup>h</sup>: heart blood sample (vena cava); Blood<sup>u</sup>: site of blood sample unspecified.

Case	Date of death	Age	Sex	Matrix	PMMA concentration	Other substances detected and concentration (where available)	Adverse events/ Autopsy findings	Additional information reported
1	Dec 2011	19	M	Blood <sup>u</sup>	2.17 mg/L	MDMA (low) Methamphetamine (low) Amphetamine (low)	Vomited, breathing difficulties.	
2	Dec 2011	30	F	Blood <sup>u</sup>	1.64 mg/L	MDMA (low) Methamphetamine (low) Amphetamine (low) Benzoylcegonine (low) Ethanol		
3	April 2012	31	M	Blood <sup>h</sup>	2.9 mg/L	Cannabis, MDMA (low) Ethanol (18 mg/dL)		Found dead having taken "Ecstasy-like" tablets called "Wheelies".
4	April 2012	26	M	Blood <sup>h</sup>	3.3 mg/L	Cannabis, MDMA (low) Ethanol (33 mg/dL)		Found dead having taken "Ecstasy-like" tablets called "Wheelies".
5	June 2012	25	M	Blood <sup>f</sup>	2.2 mg/L	MDMA (low)	Awoke from sleep and had trouble breathing.	Went to sleep having been out and taken "Ecstasy" tablet.
6	July 2012	32	F	Blood <sup>f</sup>	Not quantified (low)	PMA 1.92 mg/L Amphetamine 4.73 mg/L		Found dead having taken drugs. Had access to "Speed".

Case	Date of death	Age	Sex	Matrix	PMMA concentration	Other substances detected and concentration (where available)	Adverse events/ Autopsy findings	Additional information reported
7	May 2013	22	M	Blood <sup>f</sup>	Not quantified (low)	PMA 4.3 mg/L Cocaine (low) Cannabis Ethanol (58 mg/dL)		Found dead at home. Had access to cocaine, cannabis and MDMA.
8	Dec 2014	31	M	Blood <sup>f</sup>	6.4 mg/L	MDMA (low) Amphetamine (low) Cocaine (trace)		Found dead at home having taken "Ecstasy" the previous evening.
9	Jan 2015	28	M	Blood <sup>f</sup>	3.7 mg/L	Quetiapine (low) Cocaine (low) Amphetamine (low) Ethanol (51 mg/dL)	Described as sweating and shaking prior to death.	Found unresponsive having taken "Superman logo Ecstasy" tablets.
10	Jan 2015	30	M	Blood <sup>f</sup>	1.7 mg/L	MDMA (low) Amphetamine (low)		Collapsed at a family party. Had access to unspecified "pills"
11	Jan 2015	28	M	Blood <sup>f</sup>	3.5 mg/L	Amphetamine (low)	Found fitting and barely breathing. Had a high body temperature.	