



EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION

**Report on the Risk Assessment of 4-MTA
in the Framework of the
Joint Action on New Synthetic Drugs**

Report on the Risk Assessment of 4-MTA in the Framework of the Joint Action on New Synthetic Drugs

On 3 February 1999, the German Presidency formally notified 4-MTA for risk assessment under Article 4 of the Joint Action on new synthetic drugs of 16 June 1997.

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 to assess the health and social risks as well as the possible consequences of prohibition of 4-MTA, was held on 18-19 May 1999.

The meeting considered the following documents:

- I. Technical Annexes A and B: The Pharmacotoxicological Report on 4-MTA, Report to the EMCDDA. Doc. N° ST/SCO/12/99
- 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 4-MTA

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

4-MTA is p-methylthioamphetamine also known as 4-methylthioamphetamine. 4-MTA may be synthesised by chemical reactions similar to those used to produce MDA. Recognised precursors include 4-methylthiophenylacetic acid and 4-methylthiobenzaldehyde. Other reagents include nitroethane and n-butylamine. 4-MTA was originally synthesised as a potential antidepressant but at present it has no therapeutic use.

2. PHARMACEUTICAL DESCRIPTION

4-MTA is sold as tablets for oral consumption. Their street name is 'flatliners', 'S-5' or 'MK'. They are usually sold as a form of 'ecstasy'.

3. HEALTH RISKS

(Documents I and II)

3.1 Individual Health Risks

(a) Acute Effects

The major acute neuropharmacological effect of 4-MTA in the rat is an increased release of serotonin, an inhibition of serotonin uptake and of monoamine oxidase A. This combination of effects results in a pharmacological profile which gives rise to concern. The limited experimental data (from only 4 studies) indicates a weak effect on dopamine and noradrenaline which is consistent with the results of a study with a single dose of 4-MTA in the rat which showed no evidence of neurotoxicity after one week. No study of the effects of multiple dosing with 4-MTA exists either in rodents or in non-human primates recognised as being a more appropriate model of potential neurotoxicity in humans. Studies in animals

indicate a rapid onset of action which is in contrast to the observations from users and clinical cases. Animal studies have shown convulsive effects which might lead to respiratory depression. Co-administration of ketamine increased the toxicity of 4-MTA in mice. Standard toxicity data on 4-MTA eg single dose, repeated dose toxicities, reproductive toxicity, teratogenicity, and on mutagenic and carcinogenic potential are all lacking. Nitro-derivatives which might be produced during the synthesis of 4-MTA, may also contribute to toxicity.

(b) Clinical Effects

4-MTA has been associated with 5 deaths: 4 in the UK and 1 in the Netherlands. 4-MTA was the only drug detected in one death, in the others it was found in combination with other drugs (MDMA, amphetamine, alcohol, methadone). Preliminary evaluation of the deaths suggests that some of the symptomatology described could be related to the 'serotonin syndrome'¹ leading to respiratory depression, which appears to be the main cause of death. One explanation could be that the combination of drugs is important. Alcohol would also be expected to contribute to respiratory depression. Ten non-fatal overdoses, nine requiring hospitalisation, have been reported: five from the UK and five from Belgium. Respiratory collapse seems to be a feature common to some of these cases also. In three UK cases, other amphetamines were detected in body fluids. The risk of overdose may be linked to the slow onset of effects, compared to MDMA, and the possibility that users take more 'pills' in the belief that that initial dose was too low.

(c) Dependence

There have been no systematic studies of dependence potential in animals or in humans. In drug discrimination studies in rats, 4-MTA has shown similar properties to MDMA. The weak dopamine effect would tend to indicate a low dependence potential because of the central reinforcing role of dopamine release.

(d) Psychological Effects

There is no systematic data on the neuropsychological effects in humans. Limited animal data suggest effects similar to the 'entactogen'² class which are different to amphetamine-type stimulant and to hallucinogenic (LSD) effects. Anecdotal reports from experienced 'ecstasy' users (who may not be representative for all such users), although not entirely consistent, indicate that it has stronger and longer lasting effects than 'ecstasy', and that it has frequently more unpleasant effects than 'ecstasy'. The effects reported in the Netherlands by a small number of users are the combination of a peaceful and calm feeling and a stimulating effect, which is neither energizing nor psychedelic, but it strongly hampers sleep. The negative effects reported by users and healthcare professionals in a number of countries include: nausea, nystagmus, hyperthermia, pressure on the eyeball, thirst, shivering, confusion, memory loss, coma, and heart attack. Amnesic effects lasting several hours have been reported. This long duration of action linked to the half-life of the drug may have implications for the ability to drive and use machinery.

¹ The 'serotonin syndrome' is a hyperserotonergic state which is a very dangerous and a potentially fatal side effect of serotonergic enhancing drugs. If such drugs are not discontinued, the condition can progress rapidly to a more serious state and become fatal. The symptoms of the serotonin syndrome are: euphoria, drowsiness, sustained rapid eye movement, overreaction of the reflexes, rapid muscle contraction and relaxation in the ankle causing abnormal movements of the foot, clumsiness, restlessness, feeling drunk and dizzy, muscle contraction and relaxation in the jaw, sweating, intoxication, muscle twitching, rigidity, high body temperature, mental status changes are frequent (including confusion and hypomania – a 'happy drunk' state), shivering.

² Dr David Nichols coined the term 'entactogen' for drugs such as MDMA. The entactogenic effect of the drug is that it acts as an emotional brace reflected in the drug's ability to facilitate the retrieval of inner material and enhance introspective states. It means essentially 'to produce a touching within' (Nichols). In the words of a user of MDMA, it provides a sense that the world is sort of 'an okay place to be'.

3.2 Public Health Risks

(a) Availability and Quality

4-MTA has been identified in six Member States, and in Australia, although seizures and clinical cases have been found mainly in three States (Belgium, UK and The Netherlands). In two States, it appears to have been available in sporadic batches, rather than on the consistent basis reported by the third. In some cases, 4-MTA is the only ingredient ('flatliners') while in others caffeine is encountered ('S-5's'). On the basis of limited information, tablets typically contain 100-130 milligrammes of 4-MTA.

(b) Knowledge and Perception of 4-MTA Among Users

Knowledge of 4-MTA is low among users and tablets containing it are generally believed to be a type of 'ecstasy'. These 'pills' have been perceived as a particularly strong, and long-lasting, type of 'ecstasy' by atypical 'innovators'³, who have a particular interest in experimenting. Among more general 'ecstasy' users, there is anecdotal evidence of an increasingly negative image associated with 'flatliners' and 'S5s'. Paradoxically, media coverage that reports 4-MTA as an 'extra strong, 'ecstasy'-type' drug may inadvertently generate awareness that stimulates use amongst 'ecstasy' users.

(c) Prevalence and Patterns of Use

Prevalence of (inadvertent) use of 4-MTA depends on the extent to which it is sold as a special type of 'ecstasy'. It is believed to form only a very small proportion of the 'ecstasy' market. Patterns of use are the same as for 'ecstasy', which appears to be experimental or occasional rather than heavy. There appears to be a small proportion of heavy users of 4-MTA.

(d) Characteristics and Behaviours of Users

Information on users of 'ecstasy' indicate that they are primarily young people aged between 16 and 30 with a more equal gender ratio than observed with other illicit drugs. Use is likely to be in combination with other party drugs such as amphetamines, cannabis and alcohol. The limited information available suggests that the people who are most likely to use 4-MTA knowingly, are 'innovators' who are often perceived as 'deviant'. Other people who may try 'flatliners' are regular 'ecstasy' users who are more integrated into the social system and are less deviant than 'innovators'.

(e) Indicators of Health Consequences

Information on the health consequences in the population are limited to those stated in 3.1.b. It is noteworthy that these adverse effects have been reported within a nine-months period and with an apparently small population of users. No information on the long-term consequences of 4-MTA use is available.

(f) Context of Use

4-MTA is taken in the context of an 'ecstasy' culture in which prior expectations exist with regard to the timing of effects. Consequently, the delayed effects of 4-MTA may be perceived

³ 'Innovators' are a category of drug users who are often perceived as deviant, have cosmopolitan social relationship and may communicate regularly with a clique of other geographically dispersed innovators. They fulfil a gatekeeping role for information about new drugs.

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

Some experienced 'ecstasy' users are a channel for the dissemination of information on 4-MTA. For young people outside of the 'ecstasy'-using population there seems to be a very low probability of coming into contact with 4-MTA under present conditions.

There is no indication that 4-MTA is widely sought after, or likely to grow in popularity. The contrary appears to be the case. The negative effects that have been described and attributed to 'flatliners' (such as: nausea, headaches and delayed effects) indicate a low likelihood that 'flatliners' will grow in popularity, or become widely used. 'Grapevine news' of deaths and intoxications associated with 'flatliners' contribute to its negative image.

A proportion of more 'innovative' drug users appear to be motivated to use 'flatliners' by a desire to experience the full diversity of sensations. The number of 'innovators' is not known but they are not an insignificant group.

Increased testing services, informed Internet advice, and peer education may produce more discrimination in the 'ecstasy' market.

Little is known of the use of 4-MTA in other settings. It has been suggested that a small minority of drug users, who seek specific effects, might be using 4-MTA in their homes.

4.1.1 Social Consequences

There is no evidence specifically on 4-MTA. 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. On the basis of comparison with MDMA, and given that 4-MTA constitutes a small proportion of the much broader 'ecstasy' market, it is very unlikely that there are any significant harmful social consequences for the user that could be attributed specifically to the use of 4-MTA.

4.1.2 Consequences for the Social Behaviour of the User

There is no evidence specifically on 4-MTA and consequences linked to disorderly conduct, acquisitive crime or violence. However, it might be considered even more unlikely than with MDMA that there is any important link between the use of 4-MTA and such consequences. The effect on driving is unknown but the long duration of action of 4-MTA is a matter of concern.

4.1.3 Other Social Consequences

There is no indication that 4-MTA 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

Manufacture, trafficking and distribution of 4-MTA is unknown to the law enforcement authorities of eleven Member States. Trafficking and distribution of 4-MTA is known in four Member States: Belgium, Germany, the Netherlands and the United Kingdom. One Member State has information on the role of organised crime in the production, trafficking and distribution of 4-MTA.

Three Member States, Belgium, the United Kingdom and the Netherlands, seized considerable amounts of 4-MTA tablets, although these amounts were limited to single seizures only and one Member State, Germany, seized small quantities. In two Member States, trafficking of 4-MTA was found in combination with other illegal substances. According to some reports, this is a growing tendency.

The seizures of considerable amounts in Belgium, the United Kingdom and the Netherlands suggest an involvement of organised crime in the production of, and trafficking in, these amounts, although there is no further information for the time being to confirm this.

5. POSSIBLE CONSEQUENCES OF PROHIBITION

5.1 Legal Status

An analysis of the legal status of 4-MTA in the 15 Member States shows that only in Sweden is the drug controlled permanently. In the Netherlands, following the assessment of the Coordination Center for Assessment and Monitoring of New Drugs of Misuse (CAM), options being considered include the placing of 4-MTA within the Opium Act for a period of one year, or the use of medicines legislation as a means of control. In Germany, 4-MTA has been provisionally controlled under the Narcotics Act, for a one-year period. Recently, the Bundeskriminalamt (BKA) has carried out a risk assessment. In January 1999, the German Expert Board endorsed the permanent control of 4-MTA. The amendment of the narcotics regulation is scheduled to come into operation during 1999. In France, 4-MTA is under immediate review. Steps are being taken in the UK to schedule 4-MTA under the Misuse of Drugs Act.

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 4-MTA and in view of the fact that the acute hazards of 4-MTA were generally not considered as less serious, there is little scope for an alternative to prohibition as a measure of control. The possibility of bringing the substance under the regulations for the control of medicines was the only alternative considered. Doubts were expressed as to whether this approach was the most appropriate method of control. Exempting 4-MTA from legal control would send an inaccurate message about the comparative safety of the substance.

In accepting prohibition of 4-MTA as the most viable 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 realistic hazards of the substance was expressed by the meeting. Such an effort

should specifically be directed at informing users of 4-MTA of the long latency period to prevent them from inadvertently taking overdoses.

The opinion was also expressed that the application of criminal law should specifically be directed at the supply level (producers and distributors) of 4-MTA. Marginalisation of users should be avoided as much as possible.

The meeting noted that since 4-MTA is part of the larger 'ecstasy' market, prohibition is unlikely to have a significant impact on the availability and usage of 'ecstasy' in general. It was also suggested that one consequence of prohibition might be to stimulate the search for newer synthetic drugs.

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 4-methylthioamphetamine and in accordance with Article 4 of the Joint Action submit the following conclusions:

6.1 The scientific evidence submitted to the meeting shows that 4-methylthio-amphetamine (4-MTA) is a potent psychoactive agent which rapidly releases serotonin and inhibits monoamine oxidase A activity. It has been associated with five deaths within the EU. Ten non-fatal cases, nine requiring hospitalisation and resuscitation, have been reported from the UK and Belgium. 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. Respiratory collapse has been reported in some cases. A delayed onset of action apparently increases the risk of overdose and combination with alcohol, MDMA, amphetamines or ephedrine also appears to increase the risks. Since the drug inhibits monoamine oxidase A, a serious interaction with certain foods could occur. Toxicity data normally used to assess the health effects of a new chemical are not available for 4-MTA.

The expert participants noted that 4-MTA had been identified in 6 Member States and also in Australia. Reports suggest that 4-MTA is sold and consumed as 'ecstasy'. Anecdotal reports suggest that this drug may be less attractive than MDMA to users because of its unpleasant effects.

Compared to MDMA, and also to MBDB, 4-MTA appears to be associated with a higher risk of acute effects including adverse reactions and overdosage. The long-term risk of neurotoxicity of 4-MTA on its own is, like MBDB, possibly lower than for MDMA but as in the case of MBDB no data is available.

6.2 Arising from 6.1 and because 4-MTA is the sulphur analogue of amphetamines already subject to control in 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 4-MTA under control should not inhibit the gathering of information about drugs on the market and the dissemination of accurate information on 4-MTA to users and to relevant professionals. The risk of overdosing due to the delayed onset of action should be highlighted, as should the risks of mixing it with alcohol, MDMA, amphetamines, ephedrine products and certain tyramine rich foods (MAOI effects).

6.3 The major chemical precursors of 4-MTA, namely methylthiobenzaldehyde and methylthiophenylacetic acid 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 closely examine the situation of those precursor chemicals which have been found in the manufacture of 4-MTA and which are not yet subject to any measure of surveillance.

- 6.4** The meeting recommends 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 4-MTA be included within the UNDCP proficiency testing programme. One opinion was, that as part of the Early Warning System specific testing of 'pills' available on the market should be possible, in order to inform potential users of the actual composition of those 'pills'.

Lisbon, 19 May 1999

Annex 1: List of participants
Annex 2: Agenda