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for Drugs and Drug Addiction

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EMCDDA
RISK ASSESSMENTS

Report on the risk assessment of TMA-2 in the framework of the joint action on new synthetic drugs

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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 TMA-2 (2,4,5-trimethoxyamphetamine) in this publication. 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 ([1]).

The meeting to assess the risks of TMA-2 was convened under the auspices of the Scientific Committee of the EMCDDA and was held on 1 April 2003 at the Centre's headquarters in Lisbon. The meeting produced a formal 'Report on the risk assessment of TMA-2 in the framework of the joint action on new synthetic drugs', which was adopted the same day. As foreseen in the joint action, the report was submitted without delay to the European Commission and to the Greek Presidency of the Horizontal Working Party on Drugs of the Council of the EU for further action.

As a result, on 27 November 2003, the Council adopted the decision ([2]) to submit 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 into their national law, in compliance with their obligations under the 1971 United Nations (UN) Convention on Psychotropic Substances.

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 is also encouraging to see that strong cooperation has developed over recent years 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 (EMEA) and the European Commission. In particular, I would like to underline the excellent work done by the EMCDDA's early-warning system via the Reitox network of national focal points and through Europol's national units. The dedication of all partners will be crucial in the successful implementation of the new Council decision proposed by the

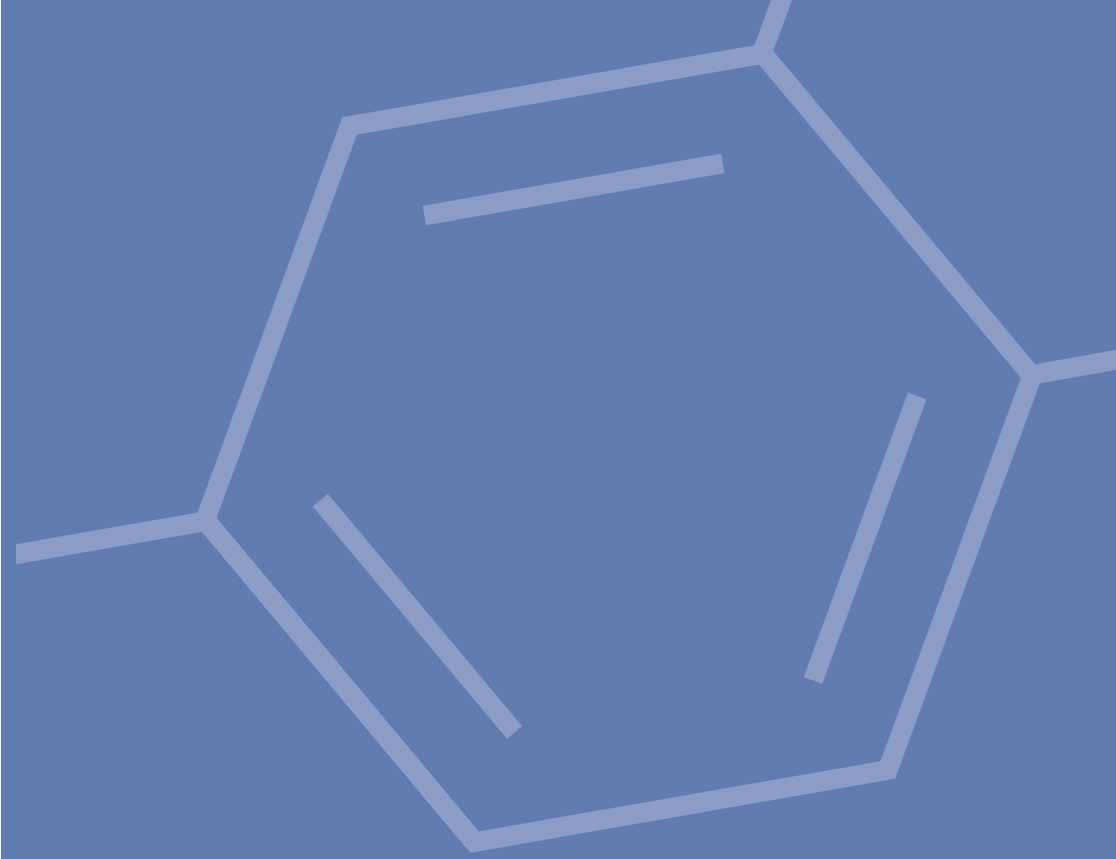
([1]) Joint action concerning the 'information exchange, risk assessment and the control of new synthetic drugs' (OJ L 167, 25.6.1997). A joint action is a decision adopted unanimously by the EU Member States within the framework of the third pillar of the Treaty on European Union (cooperation in the 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).

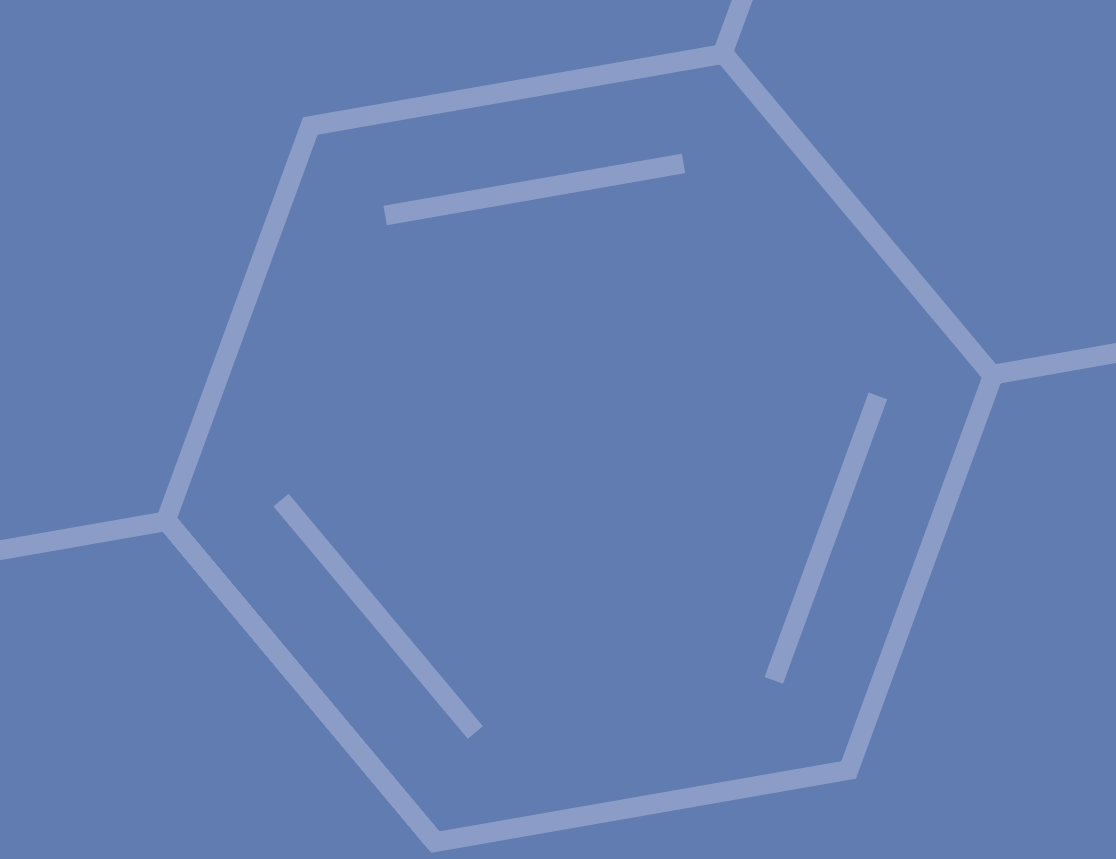
([2]) OJ L 321, 6.12.2003, pp. 64–65.

Commission to replace the 1997 joint action on new synthetic drugs. This initiative is directly related to the outcome of the external evaluation of the joint action undertaken by the Commission as stipulated by the European Union action plan on drugs 2000–04. The new legal instrument aims to clarify the definitions and procedures and extend the scope to all new synthetic drugs and new narcotic drugs alike.

I would like to thank all those who participated in the risk assessment process for TMA-2 for the high quality of the work carried out. This makes a valuable scientific contribution, validated at a European level, and, as such, gives proven support to political decision-making.

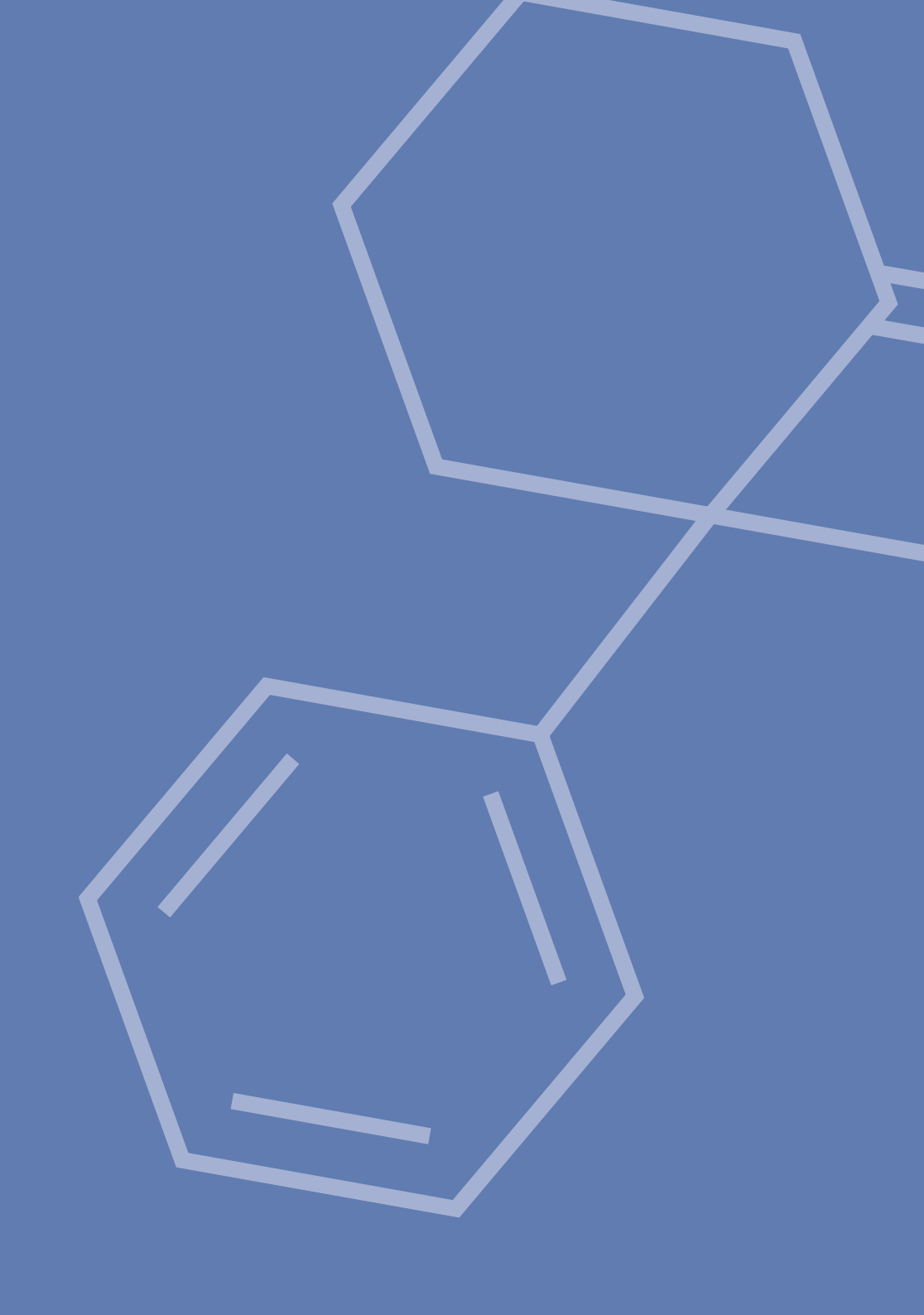
Georges Estievenart
Executive Director, EMCDDA





Abbreviations

2C-B	2,5-dimethoxy-4-bromophenethylamine
2C-I	2,5-dimethoxy-4-iodophenethylamine
2C-T	2,5-dimethoxy-4-methylthiophenethylamine
2C-T-2	2,5-dimethoxy-4-ethylthiophenethylamine
2C-T-7	2,5-dimethoxy-4-(n)-propylthiophenethylamine
bpm	beats per minute
DOB	2,5-dimethoxy-4-bromoamphetamine
DOM	2,5-dimethoxy-4-methylamphetamine
ECG	electrocardiography
EcoG	electrocorticography
5-HT	5-hydroxytryptamine (serotonin)
i.p.	intraperitoneal
i.m.	intramuscular
i.v.	intravenous
LD50	lethal dose for 50 % of animals tested
LSD	lysergic acid diethylamide
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
Mescaline	3,4,5-trimethoxyphenethylamine
MDMA	3,4-methylenedioxy-N-methylamphetamine
PMMA	para-methoxymethylamphetamine
SSRI	selective serotonin reuptake inhibitor
TMA	3,4,5-trimethoxyamphetamine
TMA-2	2,4,5-trimethoxyamphetamine



Introduction

Since the adoption by the Council in June 1997 of the joint action on the information exchange, risk assessment and control of new synthetic drugs, TMA-2 (2,4,5-trimethoxyamphetamine) is the ninth substance to be subjected to risk assessment.

Synthesised in 1947, TMA-2 is one of the numerous 'new synthetic drugs' with no legitimate therapeutic use that are described in Shulgin's *Pikhal* (Shulgin and Shulgin, 1991). TMA-2 can be produced from the active agent asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene), which is extracted from the rhizome of the plant *Acorus calamus*. The precursor asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene) is widely used as an active principle in food flavourings. TMA-2 has the structural characteristics of amphetamines, which are associated with hallucinogenic and stimulant actions. It is an analogue that is very close to TMA (3,4,5-trimethoxyamphetamine) but is 10 times more potent (20 mg of TMA-2 induces the same hallucinogenic effects as 200 mg of TMA). Therefore it carries potential risks common to TMA and other hallucinogenic substances (e.g. DOM, DOB) already classified in Schedule I of the 1971 United Nations Convention on Psychotropic Substances.

The specific scientific risk assessment of TMA-2 has been extremely difficult, due to the lack of peer-reviewed scientific data. There are, however, some limited data from studies carried out in the 1970s and 1980s. An overview of the pharmacology, toxicology, clinical experience and individual health and psychological risks of TMA-2 use was compiled by Michel Mallaret of the Centre d'évaluation et d'information sur la pharmacodépendance, Centre hospitalier universitaire, Grenoble. Moreover, Mallaret performed an original study on the toxic effects of TMA-2 in rats. This overview was further extended by a review, completed by the EMCDDA and Europol, of the pharmacotoxicological, sociological and criminological information available on TMA-2. Information based on analogy to related compounds, such as TMA, was also utilised for this assessment.

The members 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, met in Lisbon on 1 April 2003 to examine the health and social risks of TMA-2, as well as the possible consequences of its prohibition. The conclusions and recommendations of the risk assessment report were prepared and adopted the same day. Based on the conclusions of the report, the Council unanimously decided to adopt a decision making TMA-2 the subject of control measures in the EU Member States, as provided for under Schedules I and II of the 1971 UN Convention on Psychotropic Substances.

In the light of the risk assessments carried out since 1998, the Scientific Committee's sub-committee on synthetic drugs came to the following conclusions: the decision to have a molecule assessed often implies a lack of scientific data about its toxicity as well as its dependence potential or its implication in social disturbances; however, lack of scientific data does not guarantee that the molecule is not harmful. A principle of precaution should therefore be the rule when only limited data are available.

The Scientific Committee of the EMCDDA is aware of how difficult it is to obtain scientific data on a new drug and is currently reflecting, in the framework of its sub-committee on synthetic drugs, on the possibility of proposing an emergency temporary scheduling of the identified substance in order to allow time for collecting and producing sufficient scientific information. However, such a proposal could only be discussed within the perspective of a new Council decision modifying the current joint action on new synthetic drugs. Meanwhile, despite its limitations, the provisions of Article 4 of the joint action have been implemented for the risk assessment of TMA-2.

As Chairperson and Vice-Chairperson 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 EMCDDA, in particular Alain Wallon, Lena Westberg, Deborah Olszewski and Roumen Sedefov, who worked hard before, during and after the meetings to finalise the reports in order to provide detailed and precise conclusions and ensure a speedy completion of the project. 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

Council decision

Council Decision 2003/847/JHA of 27 November 2003 concerning control measures and criminal sanctions in respect of the new synthetic drugs 2C-I, 2C-T-2, 2C-T-7 and TMA-2

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on European Union,

Having regard to Council Joint Action 97/396/JHA of 16 June 1997 concerning the information exchange, risk assessment and the control of new synthetic drugs ([3]), and in particular Article 5(1) thereof,

Having regard to the initiative of the Italian Republic,

Whereas:

(1) Risk assessment reports on 2C-I (2,5-dimethoxy-4-iodophenethylamine), 2C-T-2 (2,5-dimethoxy-4-ethylthiophenethylamine), 2C-T-7 (2,5-dimethoxy-4-(n)-propylthiophenethylamine), TMA-2 (2,4,5-trimethoxyamphetamine) were 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) 2C-I, 2C-T-2, 2C-T-7 and TMA-2 are amphetamine derivatives having structural features of phenethylamines, which are associated with hallucinogenic and stimulant activity. 2C-I, 2C-T-2, 2C-T-7 and TMA-2 have not been reported to be associated with fatal or non-fatal intoxication within the Community. However, 2C-I, 2C-T-2, 2C-T-7 and TMA-2 are hallucinogenic drugs that carry potential risks common to other hallucinogenic substances such as 2C-B, DOB, TMA and DOM, already classified in Schedules I or II to the 1971 United Nations Convention on Psychotropic Substances. Therefore a risk of acute or chronic toxicity cannot be excluded.

(3) 2C-I, 2C-T-2, 2C-T-7 and TMA-2 are not currently listed in any of the Schedules to the 1971 United Nations Convention on Psychotropic Substances.

([3]) OJ L 167, 25.6.1997, p. 1.

(4) At present, 2C-I and 2C-T-2 are controlled under the national drugs legislation in five Member States; 2C-T-7 and TMA-2 are controlled in four Member States.

(5) 2C-I, 2C-T-2, 2C-T-7 and TMA-2 have no therapeutic value or industrial use.

(6) 2C-I has been identified in four Member States; 2C-T-2 and 2C-T-7 have been identified in six Member States; TMA-2 has been identified in five Member States. At present one Member State has reported one case of international trafficking of 2C-T-2 involving two Member States; no international trafficking of 2C-I, 2C-T-7 and TMA-2 has been reported. Laboratories involving the production of 2C-I, 2C-T-2, 2C-T-7 and TMA-2 have been seized in three Member States. In one of these Member States, the seizure of a large amount of the intermediate precursor 2C-H and documentation suggests the production of 2C-I. The major chemical precursors of 2C-I, 2C-T-2, 2C-T-7 and TMA-2 are commercially available.

(7) 2C-I, 2C-T-2, 2C-T-7 and TMA-2 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 United Nations 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 2C-I (2,5-dimethoxy-4-iodophenethylamine), 2C-T-2 (2,5-dimethoxy-4-ethylthiophenethylamine), 2C-T-7 (2,5-dimethoxy-4-(n)-propylthiophenethylamine) and TMA-2 (2,4,5-trimethoxyamphetamine) to control measures and criminal penalties, as provided for under their legislation complying with their obligations under the 1971 United Nations Convention on Psychotropic Substances 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 General Secretariat of the Council and the Commission of the measures they have taken.

Article 3

This decision shall be published in the *Official Journal of the European Union*.

It shall take effect on the day following that of its publication.

Done at Brussels, 27 November 2003.

For the Council
The President
R. Castelli

Chapter 1
Report on the risk assessment of TMA-2 in the framework of the joint action on new synthetic drugs

On 12 December 2002, the Horizontal Working Party on Drugs (HWPD) of the Council of the European Union decided that risk assessment of four new synthetic drugs, 2C-T-2, 2C-T-7, 2C-I and TMA-2, should be initiated. On 20 December 2002, in accordance with practice under the 1997 joint action, the Danish Presidency formally notified the EMCDDA of the HWPD's decision to submit 2C-T-2, 2C-T-7, 2C-I and TMA-2 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, was held on 1 April 2003 to assess the health and social risks of TMA-2 as well as the possible consequences of its prohibition.

The meeting considered the following documents:

(i) Review of the pharmacotoxicological data for the risk assessment of TMA-2; report to the EMCDDA
(ii) Public health risks: epidemiological evidence; EMCDDA
(iii) Sociological/criminological evidence; EMCDDA
(iv) Europol contribution to the risk assessment on TMA-2

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

Chemical description

TMA-2 is 2,4,5-trimethoxyamphetamine. According to the synthesis protocol described by Shulgin and Shulgin (1991), the main precursor in the synthesis of TMA-2 is 2,4,5-trimethoxybenzaldehyde, which is available commercially. Additional

substances needed for the synthesis are: nitroethane, anhydrous ammonium acetate, MeOH. The intermediate substance is 2-nitro-1-(2,4,5-trimethoxyphenyl) propene (yellow crystals). An oily precipitate is washed and dried to produce 2,4,5-trimethoxyamphetamine (TMA-2) hydrochloride in the form of white crystals.

TMA-2 is a synthetic drug that can also be produced from the active agent asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene), which is extracted from the rhizome of the plant *Acorus calamus*, the common sweet flag, which grows wild on the edges of swamps throughout America, Europe and Asia. To obtain 36.5 g of TMA-2 requires 10 kg of *Acorus calamus*. Recipes for extracting asarone and making TMA-2 are available on the Internet, together with warnings about contraindications.

The precursor asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene) ([4]) is widely used as an active agent in food flavourings. However, the United States Food and Drug Administration (FDA) considers *Acorus calamus* to be an 'unsafe herb', due to its carcinogenicity, nephrotoxicity and neurotoxicity, and its use in food is limited to a maximum concentration of 0.1 mg/kg. The Council of Europe's Committee of Experts on Flavouring Substances (CEFS) has proposed reducing this to 0.05 mg/kg for food and beverages sold in Europe ([5]).

At present, TMA-2 has no medical or industrial use.

Pharmaceutical description

TMA-2 is available in powder form, or as a red capsule (in France) or an orange capsule (in Spain). In France, there have been instances of TMA-2 being sold under the name 'TMA-2'; in other cases, the name was unknown. In the Netherlands, the Amsterdam Antennae project monitored TMA-2 under the name 'Zerox', but users did not use this name.

([4]) There are different asarones, with alpha-asarone being trans-propenyl, beta-asarone the cis-propenyl and gamma-asarone (also called euasarone) being the allyl-isomer.

([5]) The European Commission, Scientific Committee on Food SCF/CS/FLAVOUR/9 ADD1 Final, 8 January 2002.

There is no direct evidence on the routes of administration used. However, as the drug was mainly detected in capsules, the main administration route may be oral. Even though the drug has also been found in powder form, there are no reports of intranasal administration or injecting.

There are no scientific reports on TMA-2 use in combination with other drugs. However, on one Internet forum a user describes an experience of a 'phenethylamine binge' with 40 mg TMA-2 in combination with 2C-T-2 and 2C-B.

Shulgin and Nichols (1978) mention that the effective oral dose of TMA-2 for humans is between 10 and 30 mg. The original study by Shulgin involved oral administration of 20–40 mg of TMA-2. This compares to Shulgin and Nichols' recommended 'equipotent' dose of 30–50 mg for 2,5-DMA, 0.2–1 mg for DOB and 1–5 mg for DOM.

Health risks

Individual health risks

Acute effects

TMA-2 was studied in the 1970s and 1980s. However, few data are available.

TMA-2 is a 5-HT_2 receptor agonist. It inhibits the binding of D-LSD in rat brain membranes. TMA-2 has been shown to have an affinity for rat fundus 5-HT receptors and for rat cortical brain 5-HT_1 and 5-HT_2 receptors.

There are no data about the neuroendocrinology of TMA-2.

The neuro-behavioural effects of TMA-2 in rats have been studied recently (Mallaret et al., 2002). Intraperitoneal (i.p.) administration of TMA-2 in rats induces increased locomotor activity, which may be due to a moderate stimulant effect and/or to serotonin-mediated behavioural syndrome. Increased motor activity and behavioural changes occur even with low doses of TMA-2 (2 mg/kg). If the dose is increased (2–80 mg/kg), rats present a serotonin-mediated behaviour (head and trunk weaving, forepaw treading, flat body posture with hind limb abduction, salivation, hyperactivity and 'wet dog shake', etc.). It may be assumed that TMA-2 induces most

of these symptoms. The locomotor increase (which is less significant than amphetamine-induced hyperactivity) may also be due to 5-HT receptor stimulation. The highest TMA-2 doses (80 mg/kg) induce frequent clonic convulsions. A dose of 120 mg/kg was associated with fatal toxic effects ([6]).

In rats, even low i.p. doses of TMA-2 (2 mg/kg) induce a significant bradycardia, especially when the ambient temperature is low (at 18 °C, the decrease is from 500 bpm to 250 bpm). The intensity of the bradycardia does not vary much with low or high (80 mg/kg) doses of TMA-2. The arterial (systolic, diastolic and mean) blood pressure increases as the TMA-2 dose is raised. The mean systolic blood pressure may reach 165 mm Hg.

The amphetamine thermoregulatory response is usually hyperthermia, even if low doses of serotonergic agents may induce hypothermia. Whereas, in rats, when the ambient temperature is low (18 °C), low and high TMA-2 doses (2–80 mg/kg) induce significant hypothermia (33 °C; compared with 38 °C for the saline control group). The hypothermia may be due to dopaminergic D2 receptor activation. It has also been suggested that it may be due to D1 and/or serotonin receptor activation, and/or NMDA activation.

There are no data on the pharmacokinetics of TMA-2. However, one study suggests that, in rats, TMA-2 is demethylated and metabolised to a hydroquinone.

There are few animal and no human data concerning TMA-2 toxicity, reproductive toxicity, neurotoxicity, mutagenicity and carcinogenic potential.

Clinical effects

There have been no reported deaths or instances of non-fatal intoxication involving TMA-2.

After ingestion of increasing doses of TMA-2, Shulgin described hallucinogenic effects, with nausea, light tremors and modest eye dilation. He also mentions brief intestinal cramps, some diarrhoea and difficulty sleeping, but no other adverse effects.

([6]) A study in mice (Ho et al., 1970) estimated the lethal dose of TMA-2 for 50 % of the animals (LD50) as 180 mg/kg.

Dependence

Discriminative studies in animals have concluded that TMA-2 induces 'subjective' effects that seem to be different to amphetamine effects. TMA-2 induces similar effects to those produced by 2,5-dimethoxy-4-methylamphetamine, which only differs on the C 4 by a methyl group instead of a methoxy for TMA-2.

There have been no self-administration studies.

There are no data about the dependence potential of TMA-2 in humans. The only information available is a description of subjective 'potent hallucinogenic effects' by Shulgin and Shulgin (1991).

Psychological effects

There are no published data concerning the specific psychological effects of TMA-2 except anecdotal subjective user reports. Shulgin reported experiencing the 'entire package of mescaline' effects, except the intense colour enhancement (40 mg of TMA-2).

Public health risks

Availability and quality of TMA-2 on the market

TMA-2 has been identified in five EU Member States: Germany, Spain, France, the Netherlands and the UK.

Information based on early warning system databases suggests that TMA-2 is very rare. The Dutch Antennae Project found TMA-2 use in a small network of experimenters ('psychonauts') and a small group of 'frontline' clubbers.

In the Netherlands, capsules were sold in a package that also contained an advice leaflet describing the formula, effects and dangers of TMA-2.

There is no reliable information on the price of TMA-2. In France, the price for one capsule of TMA-2 was EUR 15 in 2002.

Knowledge and perception of TMA-2 among users

The level of awareness of TMA-2 is, in general, negligible, except among small esoteric subgroups of experimenters. Due to the lack of human research studies, the level of knowledge among these particular consumer subgroups (as can be seen on the Internet) appears to be more detailed than in the general scientific community. However, perceptions among consumers about the content of products sold as TMA-2 are usually based on the information provided by suppliers and the beliefs of consumers. In the absence of accurate and regulated chemical analysis, objective scientific knowledge remains extremely limited. Major information sources are Internet sites and 'dance floor pharmacology' (an informal network whereby information passes from friend to friend).

Prevalence and patterns of use

Scientific evidence of TMA-2 use in the EU is very limited. Population surveys of young adults in the EU show that a range of 1 % in Finland to 12 % in the UK have 'lifetime prevalence' of hallucinogenic substances, most commonly 'magic' mushrooms. School surveys of 15- to 16-year-olds in the EU show that 1–5 % of this age group have used LSD or other hallucinogens, compared to 10 % in the USA (EMCDDA and ESPAD).

Characteristics and behaviours of users

As mentioned above, TMA-2 users may belong to a small group of people with a pseudo-scientific interest in experimenting with hallucinogenic substances, often referred to as 'psychonauts'. There appears to be a trend among a small but significant minority of users towards broadening their repertoire of drug experiences, involving a wider range of drugs and combinations. Special concerns relate to the lack of knowledge about the drug contents and the specific harmful effects of TMA-2, either alone or in combination with other drugs.

Indicators of health consequences

With such an apparently small population of users, information on the health consequences of TMA-2 use is very limited. There is no information available on the long-term consequences of TMA-2 use.

Context of use

There is no scientific evidence about the risk factors linked to the circumstances and consumption practices associated with TMA-2.

Social risks

Sociological aspects

Young people outside of the ecstasy-using population are relatively unlikely to come into contact with TMA-2 under present conditions.

As with all illicit drug use, lack of scientific and objective information contributes towards increased risk. Firstly, inaccurate media coverage and overestimations of prevalence may promote diffusion by encouraging young people to try it. Secondly, official dissemination of inaccurate information is counterproductive, as it can undermine credibility.

A few more experimental drug users appear to be motivated by a desire to experience a wide range of sensations. It is not known how many there are in this group, but they are not insignificant.

Social consequences

There is currently no scientific evidence of negative social consequences. However, TMA-2 carries potential risks common to other hallucinogenic substances.

Consequences for the social behaviour of the user

There is no specific evidence to link the use of TMA-2 to disorderly conduct, acquisitive crime or violence.

Other social consequences

There is no indication that TMA-2 is particularly associated with any major value conflicts or has any important implications for social institutions beyond those described for similar compounds.

Criminological aspects

The law enforcement agencies of all 15 Member States reported to Europol that there is no information available that would suggest large-scale production, distribution and/or trafficking of TMA-2 or that organised crime has a role in these activities. Belgium and Italy reported that the main reason for the lack of information is that the substance is not controlled in these countries and, therefore, no records are kept by the law enforcement agencies.

Germany reported to Europol that a limited quantity of TMA-2 was produced in 1999. This related to one case only, involving a small 'kitchen-type' laboratory in Brannenburg, Bavaria. The amount seized was 4 g.

The Reitox national focal points reported to the EMCDDA on four other findings: 1.24 g in powder form was seized in the UK from a small laboratory, in April 2001, in what is believed to have been one attempt to manufacture TMA-2 for personal use; Spain reported a case of trafficking, and a seizure of 185 orange capsules, in March 2001, near the city of Valencia; in France, two samples of TMA-2 were collected through the Sintes project in August 2002 in the south-west region; in the Netherlands, DIMS has identified TMA-2 on five occasions — two samples in powder form, one sold in July 2001 and the other one in October 2002, monitored by the Amsterdam Antennae Project under the code name 'Zerox', and three capsules of TMA-2 between May and July 2001.

The total amount of TMA-2 seized in the Member States is very small when compared with the overall ecstasy seizures in the European Union (over 15 million tablets annually in recent years). Member States law enforcement agencies did not have any data on violence in connection with the production, distribution and trafficking of TMA-2.

Possible consequences of prohibition

Legal status

TMA-2 is a controlled drug in four EU Member States: Germany, Greece, Ireland and the UK.

In the UK, TMA-2 is a controlled Class A drug under the Misuse of Drugs Act 1977 and is covered by the generic definition (TMA-2 is a positional isomer of the UN-controlled drug TMA).

In Ireland, arising from a similar generic approach, the drug is classified under Schedule 1 of the Misuse of Drugs Act.

In Germany, TMA-2 is controlled under Schedule I (BtMG, September 1999).

In Greece, TMA-2 is classified under Table A of Law 1729/87.

Possible consequences of prohibition

The meeting acknowledged that TMA-2 is already controlled in four Member States. It noted that, structurally, TMA-2 is a hallucinogenic drug that seems to be comparable to substances already classified under Schedules I or II of the 1971 United Nations Convention on Psychotropic Substances. It was also noted that TMA-2 has no medical or industrial use.

Arising from the above, it was felt that there is no real alternative to prohibition as a control measure. It was generally agreed that such measures would enhance the capacity for detection and monitoring of the drug on the market and limit the potential for expansion of the supply and use of TMA-2. Another supporting argument was that exempting TMA-2 from legal controls would send an inaccurate message about the comparative safety of the substance. Increased availability of information about the drug would also stimulate the gathering and dissemination of analytical information for public health purposes.

The meeting feared that prohibition could engender stigmatisation of the small self-limiting groups of TMA-2 users. It was also felt that the lack of scientific evidence makes it very difficult to determine the possible consequences of legal controls on TMA-2.

There was a consensus of opinion that control measures should not prevent the dissemination of accurate information on TMA-2 to users and to relevant professionals

for preventive and harm reduction measures. Marginalisation of TMA-2 users should be avoided.

Conclusions

The Scientific Committee of the EMCDDA, extended with experts from the Member States and representatives of the Commission, Europol and the EMEA, have considered the health and social risks as well as the possible consequences of prohibition of TMA-2 and, in accordance with Article 4 of the joint action, submit the following conclusions.

- TMA-2 has the structural characteristics of amphetamines, which are associated with hallucinogenic and stimulant activity. This would appear to make it comparable to substances already classified in the schedules of the 1971 United Nations Convention on Psychotropic Substances, such as DOM, DOB and TMA (Schedule 1).

Specific scientific risk assessment of TMA-2 is extremely difficult, due to the lack of peer-reviewed scientific data. However, information based on analogy to DOM and TMA and some reports of animal experiments indicate the following.

- TMA-2 is a synthetic drug, synthesised from the precursor 2,4,5-trimethoxybenzaldehyde. It can also be synthesised from the precursor asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene), which is extracted from the rhizome of the plant *Acorus calamus*.
- TMA-2 is a 5-HT_2 receptor agonist.
- TMA-2 is a hallucinogenic drug that is 10 times more potent than TMA (20 mg of TMA-2 induces the same effects as 200 mg of TMA). TMA-2 is approximately 10 times less potent than DOM or DOB.
- In animal experiments, TMA-2 induces species-specific thermoregulatory responses (hypothermia) associated with bradycardia and hypertension and an experimental serotonin-mediated behavioural syndrome; in rats, convulsions only occur with the highest dose (80 mg/kg).

- Due to the lack of specific scientific evidence, acute or chronic toxicity has not been confirmed in humans, but toxic effects cannot be excluded.
- There have been no reported cases of fatal or non-fatal intoxication.
- TMA-2 showed a DOM-like abuse liability in one animal discrimination study.
- TMA-2 is used orally. No other routes of administration have been reported.
- There is no scientific evidence of negative social consequences. However, TMA-2 carries risks common to other hallucinogenic substances that are already controlled.
- TMA-2 has no current medical or industrial use.
- Seized/available material includes powder and capsules.
- There has been one reported case of international trafficking involving one EU Member State.
- TMA-2 has been identified in five EU Member States and it is controlled in four.

Recommendations

1. The meeting was strongly of the opinion that, due to its hallucinogenic/stimulant properties and potential serious risk to health, TMA-2 should be a controlled substance. However, there were some experts who felt that there was insufficient scientific evidence to make such a recommendation.

2. The meeting also recommended that any decision to place TMA-2 under control should not inhibit the gathering of information about drugs on the market and the dissemination of accurate information on TMA-2 to users and relevant professionals.

3. Both the chemical precursors of TMA-2, 2,4,5-trimethoxybenzaldehyde and asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene) are available commercially. The meeting recommended that the Drug Precursors Committee (set up under Article 10 of Regulation (EEC) No 3677/90 and Directive 92/109/EEC) should closely examine the situation regarding the two precursor chemicals that are involved in the synthesis of TMA-2.

4. The meeting reiterated its previous recommendation that, when a new synthetic drug is notified for risk assessment, arrangements be made for the provision of standard reference materials and associated analytical data to forensic and toxicology laboratories within the European Union. The meeting further recommended that TMA-2 be included in the United Nations Office on Drugs and Crime (UNODC) proficiency testing programme.

Lisbon, 1 April 2003

Chapter 2
Europol–EMCDDA progress report on TMA-2

Joint EMCDDA–Europol progress report on TMA-2 to the Horizontal Working Party on Drugs of the Council of the European Union in the framework of the joint action on new synthetic drugs

1. Since the adoption of the joint action on new synthetic drugs in June 1997 and the setting-up of the early warning system, a number of synthetic substances have been detected and monitored.

2. Depending on different variables, such as the gravity of the consequences of using a substance, the nature of the evidence, the frequency of its detection and the scale of its presence on the market (notifications and seizures), the EMCDDA and Europol:

   (a) have produced joint reports for some of these substances (when the initial estimation of risks required it); and
   (b) have continued to collect information for the others (those with less evident risks), in order to build up a complete picture.

3. On the basis of the EMCDDA–Europol joint reports, the EMCDDA's enlarged Scientific Committee was requested to carry out risk assessments on these substances. Thus, risk-assessment reports have been produced for the following substances: MBDB, 4-MTA, GHB, ketamine and PMMA.

4. Following the normal risk assessment exercises and procedures, decisions were taken to put some of these substances (4-MTA, PMMA) under control and to continue to monitor the others (MBDB, GHB, ketamine).

5. In the meantime, the EMCDDA and Europol have obtained more information on a number of substances. These are 2C-T-2, 2C-T-7, 2C-I, TMA-2, BZP, TFMPP, PMEA, DOC, 5-MeO-DMT, 5-MeO-DIPT, DXM, DPT, A-MT and ALEPH-7.

6. This report presents the current information on TMA-2.

7. The Horizontal Working Party on Drugs is requested to take note of this information and to give instructions if the substance should undergo a risk assessment.

Chemical and physical description

Chemical name: 2,4,5-trimethoxyphenylisopropylamine

Synonyms: TMA-2
2,4,5-trimethoxy-alpha-methylbenzeneethanamine
2,4,5-trimethoxy-alpha-methylphenetylamine
2,4,5-trimethoxyamphetamine
2,4,5-TMA
1-(2,4,5-trimethoxyphenyl)propan-2-ylazan (Germany)

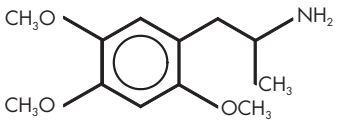
Street name: TMA-2

TMA-2 is an analogue (isomer) of the UN Schedule I substance TMA (3,4,5-trimethoxyamphetamine, a three-carbon homologue of mescaline).

Synthesis routes for TMA-2 are available on the Internet.

Molecular formula: $C_{12}H_{19}NO_3$

Chemical structure:



Pharmaceutical form: powder/crystals in capsules; also found in powder form

Route of administration, dose and duration

Route of administration: oral

Common dose range: 20–40 mg

Duration: 8–12 hours

Effects

TMA-2 has potent hallucinogenic effects (Shulgin describes an 'introspective' effect, similar to, but 10 times more potent than, mescaline). Its stimulant effects are much weaker.

Health risks

There is only a small margin between the dose needed to produce psychoactive effects and a toxic dose (Shulgin, 1976).

There have been no reported fatalities in the EU.

Legal status

As a positional isomer of the UN scheduled substance TMA (Schedule I), TMA-2 is a Class A controlled drug in the UK.

In Ireland, TMA-2 is subject to control as a Schedule I controlled drug under the Misuse of Drugs Act. This arises out of Ireland's generic approach to the control of these types of drug.

TMA-2 is also controlled in Germany under Schedule I (BtMG, September 1999).

TMA-2 is a controlled drug under Schedule II of the USA.

Reports to the EMCDDA

(A = reporting form; B = other)

UK (A): notification on 1 August 2001 of one seizure (1.24 g of TMA-2 in powder form) in June 2001.

Spain (A): notification on 5 June 2002 of one seizure (on 14 March 2001) of 185 orange capsules, 65 mg each (TMA-2 and saccharose).

France (A): notification on 5 September 2002 of one red capsule (191 mg) and 125 mg of powder (TMA-2 and saccharose) collected by Sintes.

The Netherlands (B): one case in 2001 of two capsules collected from smartshops.

Chapter 3
Review of the pharmacotoxicological data on TMA-2 ([7])

Very limited data for TMA-2 have been published in peer-reviewed scientific journals. The following review includes results from a study of TMA-2 by Mallaret et al. (2002) as well as from studies involving structurally related compounds. Furthermore, limited information from user reports has been included in accordance with the EMCDDA's *Guidelines for the risk assessment of new synthetic drugs*, which recommends the use of sources such as the media, individual user reports and unofficial publications (EMCDDA, 1999).

Chemical and pharmaceutical information

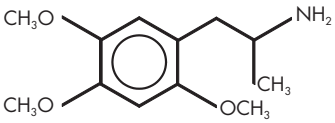
The psychoactive properties of TMA-2 (2,4,5-trimethoxyamphetamine or 2,4,5-trimethoxyphenylisopropylamine) and some other psychotomimetics were described in the late 1960s and 1970s (Shulgin et al., 1969; Ho et al., 1970; Shulgin and Nichols, 1978). The publication of *Pihkal* by Shulgin and Shulgin (1991) provided access to information about TMA-2 and some other 'designer drugs' to the wider public. That TMA-2 is designated as a 'new' synthetic drug, in the framework of the 1997 joint action, is somewhat unusual, since this molecule was first synthesised in the 1960s. However, this can be explained by the recent use of TMA-2 as a 'recreational' drug.

Chemical description

The chemical structure of TMA-2 (2,4,5-trimethoxyamphetamine) is shown in Figure 1. TMA-2 hydrochloride presents as fine white crystals or powder; the melting point is between 188.5 and 189.5 °C.

([7]) This report was written by M. Mallaret of the Centre d'évaluation et d'information sur la pharmacodépendance (CEIP; Centre hospitalier universitaire, Grenoble, France) for the risk assessment meeting on TMA-2 held in Lisbon on 31 March and 1 April 2003. Help and information was provided by Simon Elliot, J. Idampaa-Heikkila, Cécile Julien, Alain Wallon, Lena Westberg and Roumen Sedefov. The report was commissioned by the EMCDDA as a background paper for the risk assessment of the compound TMA-2. The report follows the structure of Annexes A and B to the 'Risk assessment guidelines' developed by the Scientific Committee of the EMCDDA.

Chemical structure of TMA-2



Molecular formula: $C_{12}H_{19}NO_3$
Molecular weight: 225.3

TMA (3,4,5-trimethoxyamphetamine) 'was the very first totally synthetic psychedelic phenethylamine that was found to be active in man'. The '2,4,5-trimethoxy' pattern was subsequently found and TMA-2 and its psychoactive properties were recognised by A. Shulgin in 1962. The abbreviation 'TMA-2' is derived from the nomenclature according to Shulgin and Shulgin (1991) and the '-2' part refers to the historical order of the study/discovery (Pihkal No 158). The chemical abstracts registration (CAS) number for TMA-2 is 1083-09-6.

Other TMA-2 synonyms are 2,4,5-trimethoxy-α-methylbenzeneethanamine, 2,4,5-trimethoxy-α-methylphenethylamine, 2,4,5-trimethoxyphenylisopropylamine and 2,4,5-TMA.

Methods of synthesis

According to the synthesis protocol described by Shulgin, the main precursor in the synthesis of TMA-2 is 2,4,5-trimethoxybenzaldehyde, which is commercially available (Sigma Co. catalogue). Other substances required for the synthesis are nitroethane, anhydrous ammonium acetate and MeOH. The intermediate substance is 2-nitro-1-(2,4,5-trimethoxyphenyl) propene, as yellow crystals. An oily precipitate is washed and dried to yield 2,4,5-trimethoxyamphetamine (TMA-2) hydrochloride as white crystals (Shulgin and Shulgin, 1991).

TMA-2 can also be produced from the active agent asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene), which is extracted from the rhizome of the plant *Acorus calamus*, the common sweet flag that grows wild on the edges of swamps throughout America, Europe and Asia. To obtain 36.5 g of TMA-2, 10 kg of *Acorus calamus* are necessary. Recipes for extracting asarone and making TMA-2 are available on the Internet, together with warnings about contraindications.

Identification

There is little information available about identifying TMA-2. Shulgin and Nichols (1978) compared TMA-2 and DOM by the spectrofluorometric assay of these substances (relative intensity 0.5 and 1.0 respectively). Baker et al. (1973) compared the molecular structures of TMA-2, LSD and psilocybin. There is also some information regarding the analytical profile of TMA-2 using gas chromatography with mass spectrometry (GC-MS) and proton nuclear magnetic resonance (NMR).

The Marquis reagent assay turns lime green, similar to 2C-B (Erowid, 2001).

Legitimate uses of TMA-2

There are no known licensed therapeutic or industrial uses for TMA-2.

The precursor asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene) is widely used as an active agent in food flavourings. However, the United States Food and Drug Administration (FDA) considers *Acorus calamus* to be an 'unsafe herb', due to its carcinogenicity, nephrotoxicity and neurotoxicity, and its use in food is limited to a maximum concentration of 0.1 mg/kg. The Council of Europe's Committee of Experts on Flavouring Substances (CEFS) has proposed reducing this to 0.05 mg/kg for food and beverages sold in Europe.

Pharmaceutical form

TMA-2 is available as a powder or in capsule form (red capsules in France, orange capsules in Spain). TMA-2 was sometimes sold in France ([8]) under the name 'TMA-2', but in other instances the name was unknown. In the Netherlands, the Amsterdam Antennae Project monitored TMA-2 under the name 'Zerox', but users appear not to have used this name.

TMA (3,4,5-trimethoxyamphetamine) is a synthetic drug that usually presents as a yellowish or beige powder.

([8]) There is little information about the street price of TMA-2. In the French instance, the purchase price was EUR 15 (Sintes, 2002).

Combination with other drugs

There have been no scientific reports of TMA-2's use in combination with other drugs. However, a user on one Internet forum describes an experience of a 'phenethylamine binge' with 40 mg TMA-2 in combination with 2C-T-2 and 2C-B ('the visuals were amazing ... enjoy!').

Routes of administration and dosage

There is no direct evidence about the routes of administration. However, as the drug has mainly been detected in capsules, the main administration route is probably oral. Even though the drug has also been found in powder form, there are no reports of intranasal administration or injecting.

Shulgin and Nichols (1978) described the human effective oral dose of TMA-2 as between 10 and 30 mg. The original study by Shulgin involved oral administration of between 20 and 40 mg of TMA-2. This compares to Shulgin and Nichols' recommended 'equipotent' dose of 30–50 mg for 2,5-DMA, 0.2–1 mg for DOB and 1–5 mg for DOM.

After administration of increasing doses of TMA-2, Shulgin and Shulgin (1991) described hallucinogenic effects, with 'nausea, light tremors and modest eye dilation', and 'the entire package of mescaline, missing only the intense colour enhancement'. Furthermore, 'the world is filled with distorted moving things. [With 40 mg] Very slow coming on ... Beautiful experience. Erotic, excellent ... Benign and peaceful and lovely. There were brief intestinal cramps early, and a little diarrhoea, but no other problems'.

The 'typical' dose range of the hallucinogenic TMA (3,4,5-trimethoxyamphetamine) is between 150 and 200 mg (Cox et al., 1983) taken orally or by injection. Shulgin's 'recommended' dose for TMA is 100–250 (Shulgin and Shulgin, 1991). It should be noted, however, that the accuracy of the doses reported by users depends on various factors, such as the accuracy of weighing, the user's knowledge of the actual constituents of the powder or capsule, honesty, etc.

Lower doses of TMA (50–100 g) produced dizziness, light-headedness, euphoria, garrulousness and loss of emotional inhibitions. Shulgin and Shulgin (1991) described its effects as follows.

Hallucinogenic doses produce effects similar to mescaline, including intense visual imagery, perceptual distortions, synesthesias (the melding of one sensory modality with another: 'music is seen') and dissociation from the environment. A number of amphetamine-like physiological effects occur prior to the onset of TMA's hallucinogenic actions; these can include behavioural arousal, slight motor increased reflex responses, slight tremor, transient mild headache, and nausea and vomiting, increased blood pressure and heart rate, loss of appetite and increased respiratory rate.

Higher doses of TMA produce at least one effect which does not usually occur with higher doses of mescaline — a tendency to unprovoked antisocial behaviour, manifested as anger or hostility towards others, and sometimes grandiose beliefs about oneself (Cox et al., 1983). In Canada, TMA was often sold on the street as MDA during the 1980s.

Pharmacology in animals and humans

TMA-2 was studied in the 1970s and 1980s, but there are very limited data available. Mallaret et al. (2002) studied the toxic effects of TMA-2 in Wistar rats. This multi-modal investigation was carried out in male rats (four rats in each group) and included assessments of the following categories: behaviour (locomotion, stereotypes in actimeter); electrocorticography (EcoG; cortical stainless steel screws); temperature (rectal probe); haemodynamics (heart rate and blood pressure with electrocardiographic electrodes and a femoral artery catheter). The rats were administered with five intraperitoneal (i.p.) doses of TMA-2 (2, 5, 20, 40, 80 mg/kg) versus saline (in the control group) during a two-hour period, preceded by one hour of baseline. A higher dose of TMA-2 was not tested, as 120 mg/kg is associated with fatal toxic effects. The two groups (TMA-2 and saline) were observed and weighed daily over one week before tissue fixation under anaesthesia and decapitation for brain histology. The results are expressed as mean + SD or as a percentage of the baseline and were analysed with non-parametric tests. Studies are ongoing to test the effects of the ambient temperature on body temperature.

Neuropharmacology

Barfknecht and Nichols (1971) believed there was a relation between hallucinogenic activity and lipophilicity. They considered TMA-2 to be equivalent to 20 'mescaline units' (MU). However, this supposed correspondence with MU is not generally accepted.

TMA-2 inhibits the binding of D-LSD by rat brain membranes: the IC-50 is 6.4×10^{-4} (Green et al., 1978). TMA-2 has an affinity for rat fundus 5-HT receptors (K_B = 150 nM). TMA-2 affinity (Ki) for rat cortical brain $5HT_1$ and $5HT_2$ receptors is respectively > 30 000 and 1 645 nM (Shannon et al., 1984).

Neuroendocrinology

There are no data available about TMA-2. The only study (Weltman et al., 1976) so far involved TMA (3,4,5-trimethoxyamphetamine). Single doses of 50 and 100 mg/kg of TMA administered i.p. in male albino mice induced adrenocortical and adrenomedullary stimulatory effects.

Neurobehavioural effects in animals

Otis et al. (1978) made a comparison of different drugs in rats. The results are rather surprising, since increased locomotor activity is described for a low dose of d-amphetamine (0.5 mg/kg). This relative hyperactivity decreases with the following drugs: amphetamine > TMA-2 (2.5 mg/kg) = MDA (1.25 mg/kg) > DOM (1 mg/kg) > mescaline (20 mg/kg) > LSD (0.5 mg/kg).

According to Mallaret et al. (2002), i.p. administration of TMA-2 in rats induces increased locomotor activity, which may be due to its effect as a moderate stimulant but could also be due to serotonin-mediated behavioural syndrome. Increased motor activity and behavioural changes occur even with low doses (2 mg/kg) of TMA-2 (Otis et al., 1978, mentioned 2.5 mg/kg). When the dose is increased (2–80 mg/kg), rats present a serotonin-mediated behaviour (head and trunk weaving, forepaw treading, flat body posture with hind limb abduction, salivation, hyperactivity and 'wet dog shake', etc.) (°).

(°) The 'serotonin-mediated behavioural model' (Green and Heal, 1985) includes: disperse, head and trunk weaving, piloerection, salivation, flat body posture, hind limb abduction, Straub tail, compulsive movement, random circling, body tremors, athetosis, ataxia, forepaw treading, unresponsive to visual stimuli, opisthotonus, death (with high doses).

The increase in locomotor activity (which is less significant than amphetamine-induced hyperactivity) may also be due to 5-HT receptor stimulation. The highest TMA-2 dose (80 mg/kg) induces frequent clonic convulsions. A dose of 120 mg/kg was associated with fatal toxic effects. An early study in mice (Ho et al., 1970) evaluated the lethal dose of TMA-2 for 50 of the animals (LD50) as 180 mg/kg.

Neurological effects in animals

In the Mallaret et al. (2002) study in rats, TMA-2 induced a dose-dependent decrease in the total magnitude of electrocorticograms (EcoG). The highest TMA-2 doses (80 mg/kg) induced frequent clonic convulsions (associated with spike-waves or polyspike discharges in EcoG).

Cardiovascular and thermoregulatory responses in animals

TMA (3,4,5-trimethoxyamphetamine) administered in the spine in dogs does not induce much variation in the heart rate, whereas amphetamine induces bradycardia. TMA and amphetamine induce hyperthermia (Martin et al., 1978).

In the Mallaret et al. (2002) study in rats, even low i.p. doses of TMA-2 (2 mg/kg) induced significant bradycardia, especially when the ambient temperature was low (18 °C). The decrease was from 500 bpm in the saline control group to 250 bpm for the TMA-2 group. The intensity of the bradycardia does not vary much with low or high (80 mg/kg) doses of TMA-2. The arterial (systolic, diastolic and mean) blood pressure increases as the TMA-2 dose is raised. The systolic blood pressure may reach a mean of 165 mm Hg, compared to 110 mm Hg for the saline control group.

The amphetamine thermoregulatory response is usually hyperthermia, even if low doses of serotonergic agents may induce hypothermia (ambient temperature is not usually controlled). In the Mallaret (2002) study, when the ambient temperature was low (18 °C), all doses of TMA-2, from low through to high (2–80 mg/kg), induced hypothermia (33 °C; compared with 38 °C for the saline control group). When the ambient temperature is high (28 °C), there is only a slight increase in temperature and no hypothermia. Otis et al. (1978) also found that the body temperature decreased from 36.9 °C to 34.9 °C when testing TMA-2 in rabbits.

Some of the causes of complications and deaths that have been attributed to amphetamine overdose include the sudden extreme elevation of blood pressure, acute cardiac failure and hyperthermia. In some conditions, amphetamine may induce hypothermia. Usually, amphetamine, a neurotransmitter releaser, induces tachycardia. In humans, even in low doses, amphetamine induces palpitations, increased heart rate and irregular heartbeat. In the Mallaret study, one theory is that the bradycardia may be due to TMA-2-induced hypertension.

MDMA-induced hyperthermia is known to enhance long-term MDMA neurotoxicity. Hyperthermia occurs quickly and before the locomotor hyperactivity, and it has been shown after i.p. administration of high doses of PMMA (para-methoxy-methylamphetamine) in rats (Mallaret et al., 2002). However, low i.p. doses (2 mg/kg) of PMMA in rats induce hypothermia. The ambient temperature may have considerable influence on the effects of amphetamines on body temperature. Usually, a high ambient temperature increases the amphetamine-enhanced body temperature.

Low doses of TMA-2 induce hypothermia in rabbits (Otis et al., 1978; unknown ambient temperature) and in rats (low ambient temperature: 18 °C). Compared to amphetamine, it would be unusual for there to be a hypothermic response in rats after a high and toxic dose (80 mg/kg) of TMA-2 in a low ambient temperature. The very slight increase in the TMA-2-induced body temperature in rats in a high ambient temperature (28 °C) is also unusual. Hypothermia may be due to dopaminergic D2 receptor activation. It has been suggested that hyperthermia may be due to D1 and/or serotonin receptor activation and/or NMDA activation (Liechti and Vollenweider, 2000; Mallaret et al., 2002).

Pharmacokinetics

There are no data on the pharmacokinetics of TMA-2. However, a study in rats *in vivo* (Sargent et al., 1976) suggests that TMA-2 is demethylated and metabolised to a hydroquinone.

Dependence potential in animals and humans

There are no data about the dependence potential of TMA-2 in humans. The only information available is the subjective description of the potent hallucinogenic effects

of TMA-2 by Shulgin and Shulgin (1991), which may give some indication of the abuse potential of TMA-2.

TMA (3,4,5-trimethoxyamphetamine) shows a cross-tolerance with LSD in guinea pigs (myoclonic jump) (Carvey et al., 1989).

There have been no TMA-2 self-administration studies. Only discriminative TMA-2 studies in animals are available. In one study (Glennon et al., 1985), rats were trained to discriminate between amphetamine (1 mg/kg) and saline in a fixed-ratio (FR 10), food-reinforced paradigm. TMA-2 produced amphetamine-appropriate responses. The amphetamine stimulus (1 mg/kg) only partially generalised to TMA-2. The amphetamine stimulus (1 mg/kg) did not generalise to TMA-2 (3 mg/kg) (Corrigal et al., 1992). In another study (Glennon, 1989), the amphetamine stimulus did not generalise to TMA-2. Furthermore, in the same study, the DOM (2,5-dimethoxy-4-methylamphetamine) stimulus generalised to TMA-2.

The conclusion that can be drawn from these discriminative studies is that TMA-2 induces 'subjective' effects, which seem to be different to amphetamine effects. TMA-2 induces similar effects to those induced by DOM (2,5-dimethoxy-4-methylamphetamine) ([10]).

Toxicology in animals and humans

There are no human and very little animal data on the toxicity, reproductive toxicity, neurotoxicity, mutagenicity and carcinogenic potential of TMA-2.

Toxicity in animals

In the Mallaret study in rats (2002), i.p. administration of high doses (80 mg/kg) of TMA-2 induced convulsions, which had a cortical origin, while EcoG showed spike-waves. Higher doses (120 mg/kg) induced death in two rats (serotonin syndrome). This study, however, did not evaluate a lethal dose of TMA-2 for 50 of the animals (LD50). As mentioned above, an earlier study had evaluated the LD50 in mice as 180 mg/kg (Ho et al., 1970).

([10]) The difference between DOM and TMA-2 is that, on the C 4 position, there is a methyl group for DOM instead of the methoxy group for TMA-2.

Toxicity in humans

There are no reports of toxic effects of TMA-2 in humans. For the highest dose (40 mg) used by Shulgin (Shulgin and Shulgin, 1991), he describes difficulty in sleeping, but it is impossible to distinguish between the potential stimulant effect of this substituted amphetamine and its hallucinogenic effect.

Clinical experience

Studies on street users

There have been no studies on street users. Information based on the EMCDDA early warning system database suggests that TMA-2 is very rare. In France, TMA-2 powder collected in an urban environment (not 'rave') was supposed to be 'like mescaline'; the desired effects were 'stimulation, hallucinations and introspection' (Sintes, 2002). The Dutch Antennae Project found TMA-2 in a small network of experimenters ('psychonauts') and a small group of 'frontline' clubbers. In the Netherlands, capsules were sold in a packet that also contained an advice leaflet describing the formula, effects and dangers of TMA-2.

Experimental clinical studies in humans

There have been no studies of TMA-2 in humans.

Psychological risk assessment (cognition, mood and mental functioning)

Acute and chronic effects

There are no published scientific data on the specific psychological effects of TMA-2, acute or chronic. As described above, limited anecdotal reports from users describe some subjective psychological effects (Erowid, 2001–02).

As already mentioned, after administering increasing doses of TMA-2, Shulgin and Shulgin (1991) described hallucinogenic effects with 'the entire package of mescaline, missing only the intense colour enhancement', 'beautiful experience', 'benign and peaceful and lovely'. Another user reported that 'this substance seems to enhance clear, intellectual communication and is also physically energising without being enervating. Visuals are unobtrusive but can be summoned with concentration, and can be interesting. During the peak it gets much more visually stimulating.' A

third user report concluded, 'I don't at all like this substance. It seems pretty weak to me — rather akin, but inferior, to MDA ... I have no idea whether the headache is perhaps indicative of some kind of damage but, regardless, I'm never doing this stuff again.'

International trafficking and seizures

(a) TMA-2 was seized in France in 2002 (powder/capsule).
(b) TMA-2 has been seized in the Netherlands, once in powder form (2001) and three times in capsule form (2001, 2002).
(c) TMA-2 was seized in London, in the UK, in 2001 (1.24 g in white powder form).
(d) TMA-2 was seized in Spain in 2001 (185 orange capsules).
(e) 4 g of TMA-2 was seized from a small 'kitchen-type' laboratory in Germany in 1999.
(f) Corrigal et al. (1992) reported that, 'recently, in Canada, novel amphetamine derivatives (including TMA-2) have been seized'.

Conclusions

TMA-2 has the structural characteristics of amphetamines, which are associated with hallucinogenic and stimulant activity. Therefore it seems to be comparable to substances already classified in the schedules of the 1971 United Nations Convention on Psychotropic Substances, such as DOM, DOB and TMA (Schedule I).

Specific scientific risk assessment of TMA-2 is extremely difficult, due to the lack of peer-reviewed scientific data. However, information based on analogy with DOM and TMA and some reports of animal experiments indicate the following.

- TMA-2 is a synthetic drug (precursor 2,4,5-trimethoxybenzaldehyde). It can also be synthesised from the precursor asarone (2,4,5-trimethoxyphenyl-1-propenylbenzene), which is extracted from the rhizome of the plant *Acorus calamus*.
- TMA-2 is a 5-HT_2 receptor agonist.

- TMA-2 is a hallucinogenic drug which is 10 times more potent than TMA: 20 mg of TMA-2 induces the same effects as 200 mg of TMA. TMA-2 is approximately 10 times less potent than DOM or DOB.
- In animal experiments, TMA-2 induces species-specific thermoregulatory responses (hypothermia) associated with bradycardia and hypertension and an experimental serotonin-mediated behavioural syndrome; in rats, convulsions only occur with the highest dose (80 mg/kg).
- Due to the lack of specific scientific evidence, acute or chronic toxicity of TMA-2 has not been confirmed in humans but toxic effects cannot be excluded.
- There have been no reported cases of fatal or non-fatal intoxication.
- TMA-2 showed a DOM-like abuse liability in one animal discrimination study.
- TMA-2 is used orally. No other routes of administration have been reported.
- There is no scientific evidence of negative social consequences. However, TMA-2 carries potential risks common to other hallucinogenic substances that are already controlled.
- TMA-2 has no current medical or industrial use.

Chapter 4
Sociological and criminological evidence and public health risks

Introduction

This chapter summarises the relevant data required by the Technical Annexes C and D to the 'Guidelines for the risk assessment of new synthetic drugs'. In the absence of systematic studies of the use of TMA-2, the evidence for this report is based on limited information collected from:

1. the Reitox national focal points in the 15 EU Member States,
2. Europol's contribution to the risk assessment of TMA-2,
3. published research literature,
4. telephone interviews with key experts in the field of drugs research,
5. the Internet (English-language searches),
6. youth media (English-language searches),
7. EMCDDA publications,
8. DEA documents.

The numbers in the list above are used in this chapter, in square brackets, to code general sources of information. Specific published references are provided at the end of the book.

Sociological and criminological evidence

Social consequences for the user

There is no evidence regarding the social consequences of use of TMA-2 or the effects on the social behaviour of users.

As with all illicit drug use, lack of scientific and objective information can be damaging. Firstly, inaccurate media coverage and overestimation of use may promote diffusion by encouraging young people to try the substance. Secondly, official dissemination of inaccurate information in order to prevent drug use by exaggerating

the risks may be counterproductive, as this may result in official sources losing credibility (Farrell, 1989; ESPAD, 1999; EMCDDA, 2002).

Wholesale production and distribution

Member States' law enforcement agencies did not provide data on violence in connection with the production and distribution of, and trafficking in, TMA-2. No reliable data are available on the volume of money-laundering that occurs in relation to the production of, and trafficking in, TMA-2. Member States' law enforcement agencies did not have data that would suggest that organised crime has a role in the production and distribution of, and trafficking in, TMA-2 [2].

Public health risks: epidemiological evidence

Availability and quality of the product on the market

Information based on early-warning databases suggests that TMA-2 is very rare. Ecstasy research among recreational drug users in dance and night-club settings shows that friends are the most usual source for illicit drugs (McElrath and McEvoy, 1999; Mixmag study; EMCDDA, 1997, 1999, 2002). Recipes for extracting asarone and making TMA-2 are available on the Internet, together with warnings about contraindications [5].

The total amount of TMA-2 seized in the Member States is very small when compared with overall ecstasy seizures in the European Union (over 15 million tablets annually in recent years). Law-enforcement agencies from all 15 Member States reported to Europol that there is no information available that would suggest large-scale production, distribution of and/or trafficking in TMA-2 or that organised crime has a role in these activities. Belgium and Italy reported that the main reason for their lack of information is the fact that the substance is not controlled in those countries and, therefore, no records are being kept within the law-enforcement system. Germany reported on the production, in 1999, of a limited quantity of TMA-2. This related to one case only, involving a small 'kitchen-type' laboratory in Brannenburg, Bavaria. Only Germany reported a seizure, in 1999, of TMA-2. The amount seized was 4 g and the seizure occurred in the same laboratory in Brannenburg [2].

There is little information on the street price of TMA-2. France reported an instance where the purchase price was EUR 15 [1].

Knowledge, perceptions and availability of information

Availability of information on effects of product

The main information sources are Internet sites and 'dance floor pharmacology', an informal network whereby information passes from friend to friend. The popularity of websites such as www.erowid.org shows the breadth of public interest in drugs. In general, news posted on these sites is acknowledged to be so far ahead of the curve and so readily available that official regulators use the sites to keep abreast of new drug trends [1]. Despite the prevalence of publications warning of the potential harm associated with using health information from the Internet, a systematic search of peer-reviewed literature found that there were few instances of reported harm. This may be due to an actual low risk for harm associated with the use of information available on the Internet, or to under-reporting of cases, or to bias (Crocco et al., 2000).

Level of awareness of product, effects and perceptions amongst drug consumers

There is a general absence of knowledge about TMA-2, even among clubbers with comparatively high prevalence of illicit drug consumption (Mixmag study; Murple, 2001; Schifano and Martinotti, 2002). Awareness of the drug is negligible except among a very small esoteric subgroup of experimenters who may use mescaline, DOB or 2C-B as reference drugs for experiencing a wider range of effects (Murple, 2001).

Due to a lack of human research studies, the level of knowledge among consumers, as demonstrated on the Internet, appears to be more comprehensive than it is among the general scientific community. However, perceptions among consumers about the contents of products sold as TMA-2 are usually based on the information provided by suppliers and on the typical beliefs of consumers. In the absence of accurate and regulated chemical analysis of the contents, objective scientific knowledge remains extremely limited.

Prevalence and patterns of use

Extent and frequency of use

No reliable evidence exists on the extent and frequency of use of TMA-2.

Route(s) of administration

There is no direct evidence on the routes of administration used for TMA-2. However, as the drug has generally been detected in capsule form, the main administration route could be oral. Even though the drug has also been found in powder form, there have been no reports of intranasal administration or injecting (see Chapter 3).

There are no scientific reports on TMA-2 use in combination with other drugs. However, on one Internet forum a user describes an experience of a 'phenethylamine binge' using 40 mg TMA-2 in combination with 2C-T-2 and 2C-B [5] (see Chapter 3).

Geographical distribution of use

There has been very limited evidence of TMA-2 use within the EU, although it has been reported by the Danish focal point.

Trends in prevalence and patterns of use

Population surveys of young adults in the EU show that lifetime prevalence of hallucinogenic substances, most commonly 'magic mushrooms', ranges from 1 % in Finland to 12 % in the UK. School surveys of 15- to 16-year-olds show that, in the EU, an average of 2 % of this age group have lifetime experience of LSD or other hallucinogens, compared with 10 % in the USA (ESPAD, 1999; EMCDDA, 2002).

Characteristics and behaviour of users

There is no evidence about the age, gender or social status of TMA-2 users or about the risk behaviours associated with use.

There appears to be a trend among a small but significant minority of users towards broadening their repertoire of drug experiences, involving a wider range of drugs and combinations. The publication of Shulgin and Perry's (2003) new book on plant isoquinolines may provoke a trend in experimenting with such substances.

Research has shown that, in general, people tend to use drugs as long as the positive factors outweigh the negative. It has been suggested that the ease with which a drug can be made is more significant than its illegality (Murple, 2001).

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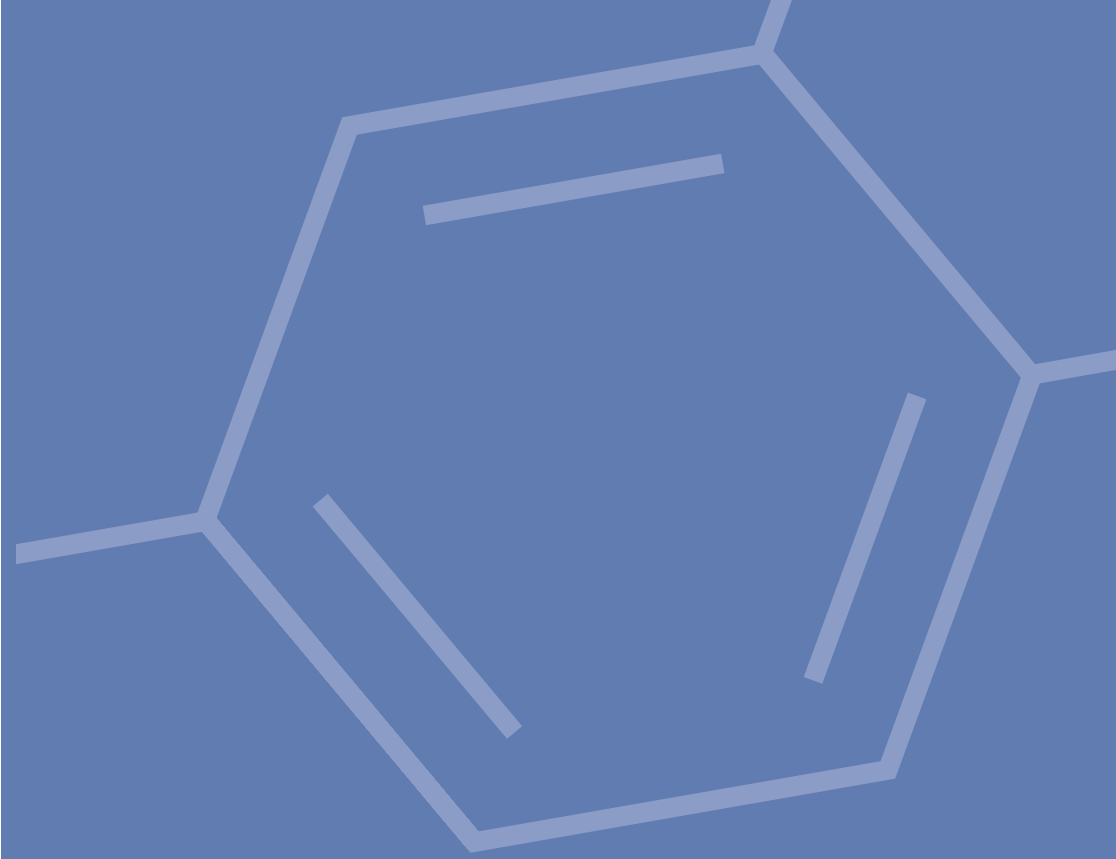

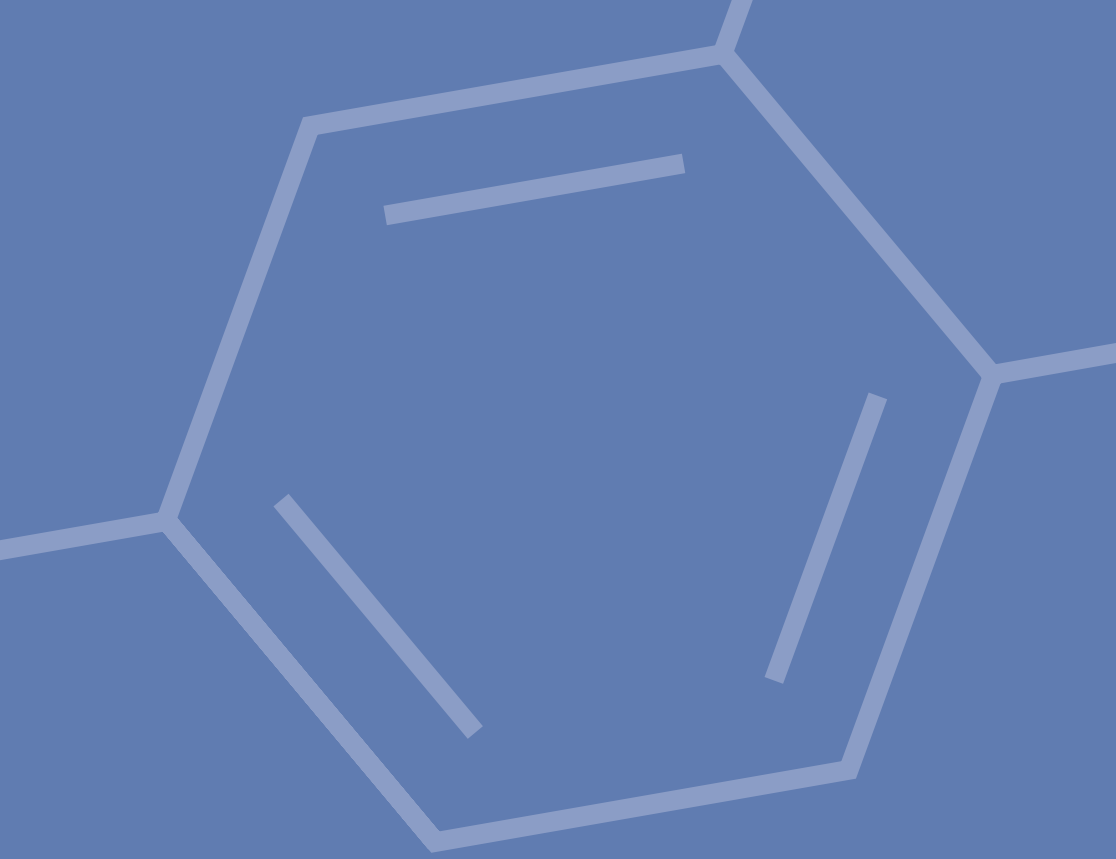

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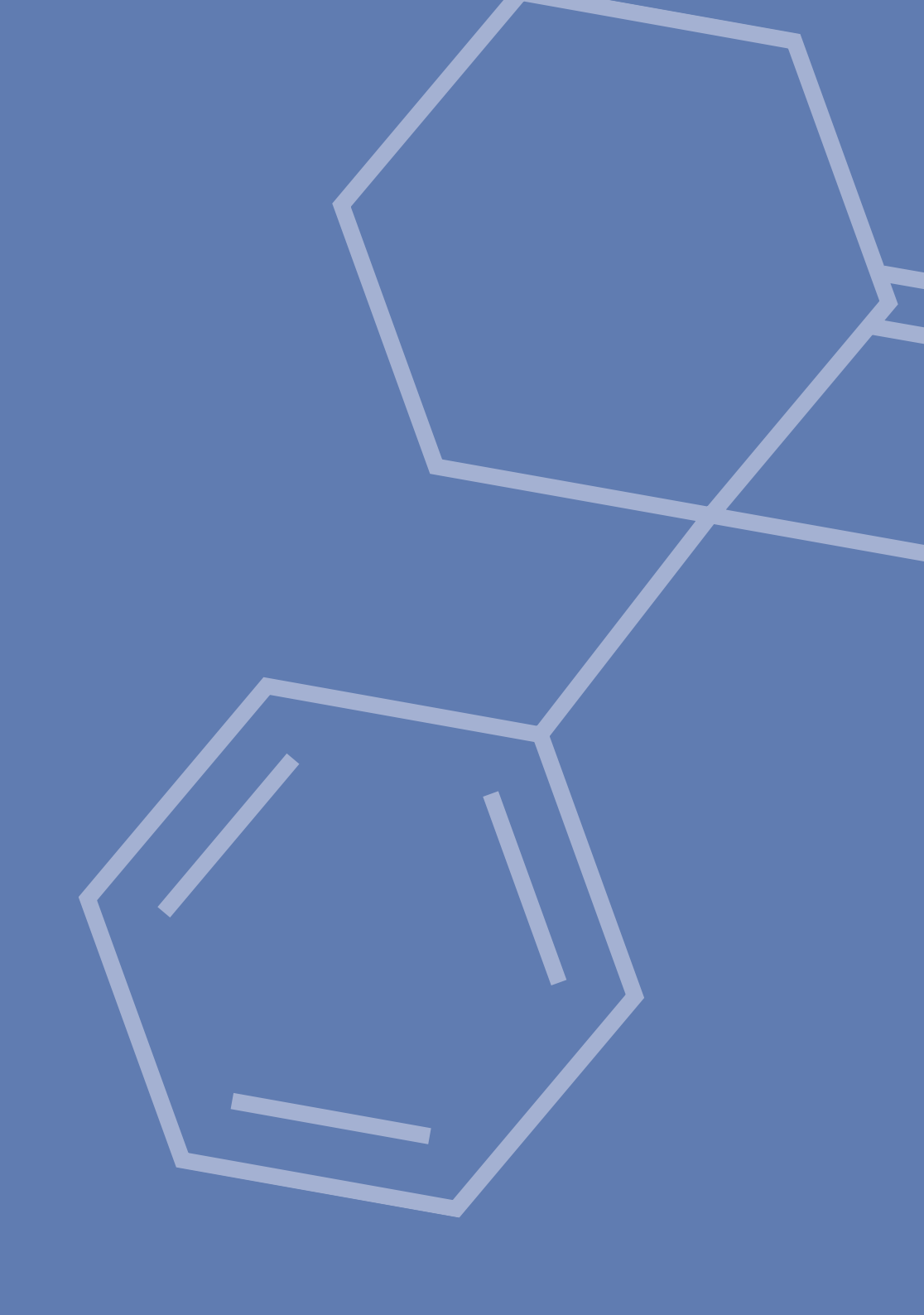

Joint action
of 16 June 1997

adopted by the Council on the basis of Article K.3 of the Treaty on European Union, concerning the information exchange, risk assessment and the control of new synthetic drugs (97/396/JHA)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on European Union, in particular Article K.3(2)(b) thereof,

Having regard to the initiative of the Netherlands,

NOTING that the Dublin European Council welcomed the progress report on drugs on 13 and 14 December 1996 and endorsed the action proposed in that report, including the proposal to tackle the problem of synthetic drugs at three levels, namely, through legislation, practical cooperation against production and trafficking and international cooperation,

REFERRING to the Joint Action 96/750/JHA of 17 December 1996, adopted by the Council on the basis of Article K.3 of the Treaty on the European Union, concerning the approximation of the laws and practices of the Member States of the European Union to combat drug addiction and to prevent and combat illegal drug trafficking ([1]),

REFERRING in particular to Article 5 of the said Joint Action, which provides that the Member States shall endeavour to draft convergent legislation to the extent necessary to make up legal ground or fill legal vacuums as regards synthetic drugs. In particular they shall promote the establishment of a rapid information system to enable such drugs to be identified as substances liable to be prohibited as soon as they appear anywhere in a Member State,

([1]) OJ L 342, 31.12.1996, p. 6.

CONSIDERING that the particular dangers inherent in the development of synthetic drugs require rapid action by the Member States,

CONSIDERING that when new synthetic drugs are not brought within the scope of criminal law in all Member States, problems may arise in the international cooperation between the judicial authorities and law enforcement agencies of the Member States owing to the fact that the offence or offences in question are not punishable under the laws of both the requesting and the requested State,

CONSIDERING that from an inventory drawn up since the adoption of the said Joint Action it can be concluded that new synthetic drugs have appeared within the Member States,

CONSIDERING that common action can be taken only on the basis of reliable information on the emergence of new synthetic drugs and the results of expert assessment of the risks caused by the use of the new synthetic drugs and implications of submitting such drugs under control,

CONSIDERING that it is therefore necessary to set up a common mechanism permitting expeditious action, in taking necessary measures or introducing controls on new synthetic drugs, on the basis of a rapid exchange of information on new synthetic drugs emerging in the Member States and the common assessment of the risks thereof,

WITHOUT PREJUDICE to the powers of the European Community,

HAS ADOPTED THIS JOINT ACTION:

Article 1

Purpose

This Joint Action aims at the creation of a mechanism for rapid exchange of information on new synthetic drugs and the assessment of their risks in order to permit

the application of the measures of control on psychotropic substances, applicable in the Member States, equally to new synthetic drugs. This mechanism will be jointly implemented in accordance with the procedures established hereunder.

Article 2

Scope

This Joint Action concerns new synthetic drugs which are not currently listed in any of the Schedules to the 1971 United Nations Convention on Psychotropic Substances, and which pose a comparable serious threat to public health as the substances listed in Schedules I or II thereto and which have a limited therapeutic value. It relates to end-products, as distinct from precursors in respect of which Council Regulation (EEC) No 3677/90 of 13 December 1990 laying down measures to be taken to discourage the diversion of certain substances to the illicit manufacture of narcotic drugs and psychotropic substances ([2]) and Council Directive 92/109/EEC of 14 December 1992 on the manufacture and the placing on the market of certain substances used in the illicit manufacture of narcotic drugs and psychotropic substances ([3]) provide for a Community regime.

Article 3

Exchange of information

1. Each Member State shall ensure that its Europol National Unit and its representative in the Reitox network provide information on the production, traffic and use of new synthetic drugs to the Europol Drugs Unit (EDU) of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), taking into account the respective mandates of these two bodies. The EDU and the EMCDDA shall collect the information received and communicate this information in an

([2]) OJ L 357, 20.12.1990, p. 1. Regulation as last amended by Commission Regulation (EEC) No 3769/92 (OJ L 383, 29.12.1992, p. 17).
([3]) OJ L 370, 19.12.1992, p. 76. Directive as amended by Directive 93/46/EEC (OJ L 159, 1.7.1993, p. 134).

appropriate manner immediately to each other and to the Europol National Units and the representatives of the Reitox-network of the Member States, to the Commission and the European Agency for the Evaluation of Medicinal Products.

2. The information referred to in paragraph 1 shall include:

(a) — a chemical and physical description, including the name under which a new synthetic drug is known,

— information on the frequency, circumstances and/or quantities in which a new synthetic drug is encountered,

— a first indication of the possible risks associated with the new synthetic drug,

and, as far as possible:

(b) — information on the chemical precursors,

— information on the mode and scope of the established or expected use of the new synthetic drug as a psychotropic substance,

— information on other use of the new synthetic drug and the extent of such use,

— further information on the risks of use of the new synthetic drug, including the health and the social risks.

Article 4

Risk assessment

1. At the request of one of the Member States or the Commission, the EMCDDA shall convene a special meeting under the auspices of the Scientific Committee extended with experts nominated by the Member States and to which representatives of the Commission, the EDU and the European Agency for the Evaluation of Medicinal Products shall be invited.

This committee shall assess the possible risks, including the health and social risks, caused by the use of, and traffic in, new synthetic drugs, and possible consequences of prohibition.

2. The risk assessment shall be carried out on the basis of information provided by the Member States, the Commission, the EMCDDA, the EDU of the European Agency for the Evaluation of Medicinal Products and taking into account all factors which, according to the 1971 United Nations Convention on Psychotropic Substances, would warrant the placing of a substance under international control.

3. On completion of the risk assessment, a report will be drawn up on the findings. In the report all aspects shall be addressed. All opinions on these aspects shall be reflected in the report.

Article 5

Procedure for bringing specific new synthetic drugs under control

1. 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 pursuant to Article 4(1) 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 are to be made subject to necessary measures of control.

   If the Commission deems it not necessary to present an initiative to have the new synthetic drug or drugs submitted to control measures, it shall present a report to the Council explaining its views.

   The Member States undertake, in accordance with the decision taken by the Council, within such delay as that decision may specify, to take the necessary measures in accordance with their national law to submit these new synthetic drugs to control measures and criminal penalties as provided under their legislation complying with their obligations under the 1971 United Nations Convention on Psychotropic Substances with respect to substances listed in Schedules I or II thereto.

2. Nothing in this Joint Action shall prevent a Member State from maintaining or introducing on its territory any national control measure it deems appropriate once a new synthetic drug has been identified by a Member State.

3. The Presidency shall each year submit a report to the Council on the implementation of the decisions adopted by the Council on the basis of paragraph 1.

Article 6

Publication and entry into force

This Joint Action shall be published in the Official Journal.
It shall enter into force on the day of its publication.

Done at Luxembourg, 16 June 1997.

For the Council
The President
H. VAN MIERLO

European Monitoring Centre for Drugs and Drug Addiction

Report on the risk assessment of TMA-2 in the framework of the joint action on new synthetic drugs

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The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is one of the decentralised agencies set up by the European Union to carry out specialised technical or scientific work.

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.

EMCDDA risk assessments are publications examining the health and social risks of individual synthetic drugs on the basis of research carried out by the agency and its partners.

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