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Europol–EMCDDA Joint Report on a new psychoactive substance: 1-(3-chlorophenyl)piperazine (mCPP)

In accordance with Article 5 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances

1. Introduction

Article 5.1 of Council Decision 2005/387/JHA ([1]) (hereinafter the 'Decision') stipulates that 'Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report (hereinafter the 'Joint Report').' The Joint Report shall be submitted to the Council, the European Medicines Agency (EMEA) and the Commission.

In August 2005, Europol and the EMCDDA examined the available information on a new psychoactive substance, 1-(3-chlorophenyl)piperazine (mCPP) through a joint assessment based upon the following criteria:

1. the amount of the material seized;
2. evidence of organised crime involvement;
3. evidence of international trafficking;
4. analogy with better-studied compounds;
5. evidence of the potential for further (rapid) spread; and
6. evidence of cases of serious intoxication or fatalities.

At that time it was agreed that the information collected so far satisfied criteria 1, 2, 3 and 5. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report as stipulated by Article 5.1 of the Decision.

2. Information collection process

In compliance with the provisions of the Decision, on 22 August 2005 Europol and the EMCDDA launched a procedure for collection of further information on mCPP, in order to prepare the Joint Report. The information was collected mainly through the networks in the Member States – the Europol national units (ENUs) and Reitox national focal points (NFPs). In addition, the EMEA collected information through the Member States' national competent authorities (NCAs) responsible for medicinal products. The information collection process was largely concluded by 30 September; however, additional information and clarifications from some Member States were received during October.

Europol asked the ENUs to provide information on:

- the level of production of mCPP in their country;
- the level of distribution of mCPP in their country;
- the level of trafficking in mCPP, whether for internal, transit, import or export purposes;
- the quantity of mCPP seized in their country and, if known, the country of origin;
- the role of organised crime, or criminal groups, in the production and distribution of, and trafficking in, mCPP in their country;
- known incidents of violence and/or money laundering relating to production and/or trafficking of mCPP in their country.

Europol received responses from 23 Member States and one Third State before or just after the six-week deadline ([2]).

EMEA asked the Member States' NCA responsible for medicinal products to provide information on whether:

- the new psychoactive substance mCPP has obtained a marketing authorisation;

([1]) Council Decision 2005/387/JHA was published in the *Official Journal of the European Union* on 20 May 2005 (L 127/32-37) and took effect the following day, i.e. on 21 May 2005.
([2]) Austria and Greece did not reply to Europol in spite of several reminders.

- the new psychoactive substance mCPP is the subject of an application for a marketing authorisation;
- a marketing authorisation that had been granted in respect of the new psychoactive substance mCPP has been suspended.

EMEA, in consultation with the EMCDDA, also requested information from the pharmacovigilance system on all spontaneously reported adverse drug reactions (ADRs) associated with the use or misuse of the antidepressant medicine trazodone (which is known to be metabolised to mCPP). A preliminary search of the patent literature revealed that mCPP could (theoretically) be used in the synthesis of four medicinal substances – trazodone, nefazodone, etoperidone or mepiprazole. Therefore, in order to confirm the situation in reality, the EMEA requested information through the Mutual Recognition Facilitation Group (MRFG) on whether or not mCPP is used in the manufacture of medicinal products containing these substances. In the event of a positive response for any of the four substances, information was requested on:

- the active substance;
- the manufacturer of the active substance;
- the invented name of the medicinal product;
- the marketing authorisation holder (MAH) for the medicinal product.

The rest of the information included in the Joint Report was collected by the EMCDDA through the Reitox early warning system of NFPs and from the World Health Organization (see section 3.5). EMCDDA received replies from all 25 Member States and Norway. Furthermore, an extensive literature review was carried out by the EMCDDA.

Thus, information included in sections 3.2 (first part), 3.3 and 3.6 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2 (second part), 3.4, 3.5, 3.6, 3.7 and 3.8. The information included in sections 3.8 (partly), 4.1, 4.2 and 4.3 was provided by the EMEA. The conclusions and recommendations of the Joint Report were prepared and agreed by the two responsible organisations – the EMCDDA and Europol – in consultation with the EMEA.

3. Information requested by Article 5.2 of the Decision

The order and titles of subsections 3.1 to 3.8 and section 4 below are exactly as they appear in Article 5.2(a) to (h) and Article 5.3(a) to (c) of the Decision. Moreover, all sections are cross-referenced with those set down in the Decision.

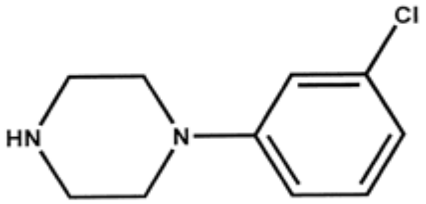
3.1 Chemical and physical description, including the name under which the new psychoactive substance is known – Article 5.2(a) of the Decision

Chemical description and names

1-(3-Chlorophenyl)piperazine is the systematic chemical name of a piperazine-derived designer drug that is better known by one of its codenames – mCPP (where 'm' stands for meta, signifying the third position of the chlorine atom on the phenyl ring, and 'CPP' stands for chlorophenylpiperazine). Other related codenames include 3CPP and 3Cl-PP ([3]). Depending on the position of the chlorine atom, other possible CPP isomers are 1-(4-chlorophenyl)piperazine (codenames pCPP (for para-CPP), 4CPP or 4Cl-PP) and 1-(2-chlorophenyl)piperazine, (codenames oCPP (for ortho-CPP), 2CPP or 2Cl-PP). As use of codenames could be confusing, they should be used only for initial orientation ([4]). The street names by which mCPP is known in the Member States are included in subsection 3.8(ii) of

([3]) The original French reporting form (dated 3 February 2005) mentions acetyl mCPP, which could be treated as a simple derivative of mCPP.
([4]) For example, CPP is also the abbreviation for the herbicide 4-chlorophenoxypropionic acid (also known as 4-CPP). A second related herbicide is 2-methyl-4-chlorophenoxypropionic acid (abbreviated to MCPP, but not mCPP). These substances are used for killing broad leaved-plants in lawns; they have a pungent smell and no psychoactive properties.

the Report. The molecular structure, formula and weight of 1-(3-chlorophenyl)piperazine are shown below.



mCPP

Molecular formula: $C_{10}H_{13}ClN_2$
Molecular weight: 196.68

Identification and analytical profile

The Chemical Abstracts Service (CAS) registry number of mCPP is 6640-24-0 and the CAS number of pCPP is 38212-33-8.

Colour screening tests: mCPP does not react to Marquis, nitroprusside or Scott's reagents.

Mass spectral data for mCPP (*m*/*z*) : 154 (base peak); 196, 156, 56, 138.

Physical description (general)

A more detailed description of the physical from of the seizures and collected ([5]) samples can be found in subsection 3.2 below.

1-(3-Chlorophenyl)piperazine is a white powder. It is widely commercially available, for example from numerous suppliers on the Internet ([6]), where it can be ordered in various quantities or in bulk as a powder or in solution (liquid form) as the monohydrochloride or dihydrochloride. Solutions of mCPP are clear, colourless or light yellow. It is reported that the purity of mCPP offered on the Internet varies between 95 % and 98 %.

The mCPP detections reported to Europol and the EMCDDA refer to the following three physical forms: tablets – found in all Member States which reported detections to the EMCDDA ([7]) and Europol; white powder – found uniquely in the Netherlands; and blue-white capsules – found only in France. The tablets were of varying weight, diameter, thickness, shape, with or without a logo and/or markings. Most often the colour of the tablets was (off-)white or beige with multicoloured flecks.

3.2 Information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance – Article 5.2(b) of the Decision

Information provided to Europol

The level of production, distribution and trafficking

([5]) Samples collected for monitoring and research purposes.
([6]) For example, from Sigma-Aldrich (UK), LLB Chem (DE), Maybridge (UK), Acros Organics (UK), Apollo Scientific Ltd (UK) Oakwood Products, Inc. (USA) and AB Chem Technologies LLC (DE). The other two CPP isomers, pCPP and oCPP, are also commercially available.
([7]) The following 18 Member States reported mCPP detections to the EMCDDA: Belgium, the Czech Republic, Denmark, Germany, Spain, Estonia, Finland, France, Hungary, Latvia, Lithuania, Luxembourg, the Netherlands, Austria, Poland, Slovenia, Sweden and the United Kingdom; as well as Norway. It should be noted that all eight seizures reported by Spain were of pCPP.

As mCPP is legally available to the chemical industry, there is no need for production of the substance by organised crime. Therefore, the processing activity of mCPP by organised crime relates only to the tabletting or encapsulating of the substance.

Two Member States, Austria and Greece did not provide any information to Europol.

Nine Member States, Cyprus, Ireland, Italy, Luxembourg, Malta, Portugal, the Slovak Republic, Slovenia and the United Kingdom reported to Europol that they made no seizures of mCPP([8]).

A total of 14 Member States and one Third State reported seizures of mCPP to Europol.

Belgium, Denmark, Estonia, Latvia, Lithuania, the Netherlands, Poland, Spain and Sweden reported minor seizures, ranging from two tablets in Poland to 73 tablets in eight seizures in Spain and approximately 200 tablets seized in five incidents in Belgium ([9]). The Netherlands reported 15 seizures, amount unspecified.

Five Member States and one Third State reported more significant seizures: one seizure of 549 tablets in the Czech Republic; four seizures in France, one of 5 115 tablets; one seizure in Finland of 25 300 tablets; 19 seizures in Germany totalling 13,000 tablets; 12 seizures in Hungary totalling 81 040 tablets; and four seizures in Norway totalling 10 000 tablets.

Most seized tablets were off-white with multicoloured spots, but seizures were also made of tablets with the 'RR' (Rolls Royce), 'Three links', 'Lacoste crocodile' and/or 'Versace' logo in France, Finland, Germany and Hungary.

The use of logos indicates that mCPP is sold in the user environment as ecstasy. One Member State (France) also reported the seizure of mCPP in capsule form. In 2 out of the 12 Hungarian seizures, tablets with the 'Versace' logo contained both mCPP and MDMA([10]).

Germany reported that, although mCPP seizures occurred throughout the country, there was a regional focus (Thuringen). Although most German reports relate to internal sale and distribution within the country, links were established in six cases to the Netherlands and in two cases to the Czech Republic. Sweden reported some seizures of tablets containing both mCPP and a related piperazine derivative (TFMPP) and indicated that the level of mCPP distribution was unknown as orders were often made via the Internet and the drugs entered the country via the postal system.

Although the majority of reports indicated that no information was available to suggest large-scale production, distribution of and/or trafficking in mCPP, Finland and Germany reported investigations in co-operation with the Netherlands concerning tabletting of mCPP and the involvement of organised crime. Enquiries, involving Europol support and forensic profiling, have thus far led to the discovery of mCPP acquisition and attempted acquisition from various sources both within and beyond the EU plus a tabletting unit situated in the Netherlands as well as sales conducted via the Internet. According to the Netherlands, the tabletting unit discovered had been producing the multicoloured mCPP tablets since early 2005 for distribution to Germany. The mCPP substance itself was sourced in India. In the Finnish

([8]) Austria, Luxembourg, the Slovak Republic, Slovenia and the United Kingdom reported seizures to the EMCDDA
([9]) Currently, a Belgian seizure of 10 000 tablets suspected to be mCPP (with a Versace logo) is undergoing forensic analysis.
([10]) Logos and additional data are recorded in the Europol Ecstasy Logo System.

case, co-operation with the Netherlands revealed information indicating the involvement of Turkish Kurds in mCPP trafficking.

Information provided to the EMCDDA

As mentioned above, most of the tablets from seizures reported to the EMCDDA were (off-) white or beige with multicoloured flecks, but a UK seizure referred to off-white tablets with green flecks, and in an Austrian, a Danish, a Spanish and a Swedish seizure the tablets were (plain) white. A second Danish seizure referred to light blue tablets.

The Dutch Drug Information Monitoring System (DIMS), which reported to the EMCDDA the highest number of collected mCPP samples (*n* = 46), described tablets of the following colours: beige (*n* = 5); white with coloured flecks (*n* = 24); white (*n* = 1), blue (*n* = 10) and light beige/white (*n* = 3). The large majority of the tablets had no logo, but three had a 'Nike' logo (not shown above). Furthermore, the DIMS reported three samples of powders containing mCPP. The French Système National d'Identification des Toxiques et Substances (SINTES) also reported on a number of collected samples (*n* = 9) and the Belgian NFP reported an analysis of mCPP-containing tablets in the framework of pill-testing during a music event in Dour.

In addition to the seizures and the samples collected for monitoring purposes, identifications of mCPP in biological samples ([11]) were also reported to the EMCDDA by Sweden and Belgium. The Swedish report refers to CPP found in a blood sample analysed by the National Board of Forensic Medicine. The sample was collected by the police from a 19-year-old man in the city of Örebro. The man indicated that he had taken 'legal ecstasy' called X4 (see section 3.4), so it is possible that the blood sample contained either mCPP or pCPP or both isomers.

The Belgian NFP reported two urine samples containing CPP (probably mCPP) taken from intoxicated individuals. However, since there were no reference materials, the exact isomer was not definitely established. In both cases more than one substance was present in the urine tested, in one of the cases cocaine, MDMA, cannabis and GHB, and in the other MDMA and MDEA.

3.3 Information on the involvement of (international) organised crime in the manufacture or trafficking of the new psychoactive substance – Article 5.2(c) of the Decision

Three Member States – Finland, Germany and the Netherlands – reported to Europol data indicating the involvement of organised crime in the acquisition, tabletting and/or trafficking of mCPP. In these instances, data related to the sourcing of mCPP tablets in the Netherlands.

Finnish information indicated the involvement of Turkish Kurds in the trafficking of mCPP.

German and Dutch information demonstrated the acquisition, tabletting and trafficking of mCPP.

Money laundering aspects

No information was received on money laundering related to the production and/or trafficking of mCPP.

Violence in connection with production, wholesale and distribution

One Member State, Finland, reported to Europol a case involving violence. In this case a person of Turkish Kurd origin coming from the Netherlands was arrested on arrival in Finland in possession of 25 300 tablets containing mCPP. As the substance is not under legislation

([11]) Biological (human) samples, e.g. body fluids (urine, blood), tissues, hair, etc.

the courier was released shortly afterwards and subsequently seriously assaulted upon his return to the Netherlands.

3.4 A first indication of the risks associated with the new psychoactive substance, including the health and social risks, and of the characteristics of users – Article 5.2(d) of the Decision

First indications of health risks

In terms of toxicity, little is known about the long- or short-term effects of mCPP. No fatal case due to, or involving, mCPP has ever been reported by a Member State. France and Belgium are the only two countries which reported intoxications involving mCPP.

In France, the users described the disorders that occurred following the ingestion of mCPP as ranging from 'light to severe'. These included nausea, vomiting, headaches and, occasionally, 'psychological discomfort' such as anxiety, depressive symptoms, feeling of being persecuted and aggressiveness. The French NFP reported that at the Dour music festival in Belgium near the French border some users suffered from hot flushes and a feeling of suffocation. Several users reported a 'quite long stimulation effect'. Two people who injected the substance reported face swelling, hot flushes and breathing difficulties.

The Belgian NFP reported on two intoxications involving mCPP, one of which, occurring in a 22-year-old man at the same music festival (Dour), resulted in coma. However, in both intoxications a number of other psychoactive substances were present (see section 3.2 above).

Despite the fact that mCPP has been used in various neurochemical research projects, the risk associated with the use of mCPP in humans has not been determined. There seems to be a wide range of opinions and 'recommendations' regarding the dosage and effects of mCPP. Furthermore, a lack of knowledge about the properties of mCPP and, often, unawareness of its presence, as well as variations in the amount of mCPP in dosage units available on the illicit market, might pose an increased risk to users. Moreover, mCPP was often found in combination with other psychoactive ingredients such as MDMA.

mCPP and MDMA are unrelated compounds, and the occurrence of the two substances in tablets is unlikely to be a consequence of accidental contamination. Nor is MDMA a synthetic impurity in the production of mCPP. The occurrence of the two substances in tablets appears to be a deliberate attempt to create a mixture. It might be assumed that the addition of mCPP is intended to potentiate or ameliorate the effects of MDMA.

In the cases where the amount of mCPP was quantified in the dosage units/tablets, it varied substantially. For example, of 16 samples quantified by the Dutch DIMS between week 37 of 2004 and week 8 of 2005 ([12]), two samples contained 8 mg mCPP or less and the remainder contained 22–46 mg. Most samples also contained another psychoactive substance (one sample contained 1 % cocaine). The majority of the samples were tablets bought as ecstasy, but two samples were powders sold as cocaine. Notably, the latest three samples (with the 'Nike' logo) detected by the DIMS during week 31 of 2005 contained substantially higher amounts of mCPP – 62, 72 and 80 mg.

The Swedish NFP reported that a tablet called X4, which can be purchased from a Swedish Internet site as 'legal ecstasy', contains a total of 150 mg of four different piperazines – mCPP, pCPP, MeOPP (1-(4-methoxyphenyl)-piperazine) and TFMPP (1-(3-trifluoromethylphenyl)piperazine). The Swedish Poison Information Centre reported that there were four requests for information regarding X4 tablets in 2004 and three further requests up to September 2005.

([12]) Sixteen samples were quantified out of the total of 18 collected: 13 samples (from week 37 to week 53 of 2004) plus five samples (from week 1 to week 8 of 2005).

The reported Danish seizures also referred to tablets with a content similar to those described as X4 (CPP or mCPP, TFMPP, MeOPP). Furthermore, two of the Hungarian seizures and the UK seizure contained both mCPP and MDMA (not quantified).

A comparison of the subjective effects of MDMA and mCPP showed that the effects of latter are not consistent. mCPP has been described as producing stimulant and hallucinogenic effects similar to those of MDMA. Euphoric but also dysphoric, anxiogenic and sedative effects have also been reported. mCPP has been shown to release adrenocorticotrophic hormone (ACTH), cortisol, prolactin and growth hormone in humans. This rise in hormone levels probably reflects serotonin receptor responsivity and may lead to changes in behaviour and mood, panic symptoms, anxiety, dysphoria and depressive symptoms. Furthermore, a study of mCPP pharmacokinetics showed a significant increase in anxiety, tremor, dizziness, sensitivity to light and noise as well as fear of loss of control.

mCPP has not shown sympathomimetic activity; it does not increase the heart rate or blood pressure and has no influence on the electrocardiogram. There is a possibility that mCPP may interact with certain medicinal products and lead to the development of a serotonin syndrome. mCPP is not known to influence cognitive functions.

Characteristic of users

mCPP tablets are in the great majority of the cases sold/bought as the popular drug ecstasy and, predictably, there have been no specific studies of the characteristics of mCPP users. However, it can be assumed that they are the same as those of the well-studied ecstasy-using population. In summary, this is predominantly a youth phenomenon, in particular of 15- to 24-year-olds, with rates of drug use higher in males than in females, predominantly from urban areas, who frequent clubs, discos and dance events.

For those users who are aware of the fact that they are consuming mCPP, it seems that this drug has no particular attractiveness. Users' reports on the Internet, confirmed by information received from the French NFP, describe mCPP as a product of little recreational interest and a source of unpleasant effects such as anxiety, panic reactions, nausea, headaches and long-lasting hangover.

3.5 Information on whether or not the new substance is currently under assessment, or has been under assessment by the UN system – Article 5.2(e) of the Decision

Within the United Nations system, assessment on the medical aspects of substances in relation to their ability to produce drug dependence is made by the Expert Committee on Drug Dependence (ECDD) of the World Health Organization (WHO). WHO advises the Commission on Narcotic Drugs (CND) whether or not to include these substances in any of the schedules of the 1961 or 1971 UN Conventions.

The WHO informed the EMCDDA that 1-(3-chlorophenyl)piperazine is currently not under assessment and has not been under assessment by the UN system.

3.6 The date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol – Article 5.2(f) of the Decision

The first official notifications about the detection of mCPP were received by the EMCDDA and Europol in February/March 2005, concerning an identification of mCPP in a sample collected by the French drug monitoring system SINTES (3 February 2005), and in March (3 March 2005), concerning an identification of CPP in a biological sample in Sweden (see section 3.2).

Without delay, the information about the two notifications was exchanged between the EMCDDA, Europol and the Member States. The Commission and the EMEA were duly informed. Subsequently, mCPP was added to the list of monitored psychoactive substances and further information about detections in seizures, biological and collected samples was

amassed and exchanged between the two responsible organisations and the Member States (see section 3.2).

3.7 Information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State – Article 5.2(g) of the Decision

1-(3-Chlorophenyl)piperazine is not controlled under the terms of the 1961 or 1971 UN Conventions in 24 Member States and in Norway.

In Greece, the substance 'CPP' is classified in Table A ([13]) of Law 1729/87 and is, therefore, subject to the same control measures that apply to, for example, cannabis, heroin, LSD or MDMA. However, the chemical formula for 'CPP' that is included in the law is [1(3 chlorophenyl) piperazine], meaning that the actual substance controlled is identical to what in this report is described as mCPP.

Although mCPP is legally available in the EU, at least three other Member States are considering control measures. The Belgian Narcotic Drug Service has taken an initiative to include mCPP in the Royal Decree on Psychotropic Substances. However, this process, if completed, could take up to a few months. Furthermore, on 9 September 2005, at an inter-ministerial meeting, the Latvian authorities decided to elaborate a draft technical regulation to include mCPP in the amendments of Cabinet Regulation 35 – Regulation on the Lists of Controlled Narcotic and Psychotropic Substances (20 January 2004). Germany also informed Europol that legislative measures to control mCPP were in preparation.

In Finland, mCPP is not controlled under the narcotic drugs legislation but is included in Annex 1 of the list of medicinal products covered by the Medicines Act (395/1987) ([14]). In justifying its decision of 25 August 2005, the National Agency for Medicines, in accordance with the Medicines Act 3 §, considers mCPP as a medicinal product for the following reasons: (a) mCPP has pharmacological effects in humans; (b) mCPP is noted to be a pharmacologically active metabolite of trazodone, which is a medicinal substance that is found on the list of medicinal products, Annex 1; (c) in Finland, a medicinal product Azona, which contains trazodone, has obtained a marketing authorisation from the National Agency of Medicines.

3.8 Further information – Article 5.2(h) of the Decision

(i) The chemical precursors that are known to have been used for the manufacture of the substance

As stated earlier in this report (see section 3.2) mCPP is legally available and there is no need for illicit production. However, it should be mentioned that there exist a number of theoretical possibilities for synthesising mCPP. The most obvious route would be to react piperazine with *m*-dichlorobenzene. Another method would be to react *m*-chloroaniline with bis(2-chloroethyl)amine. A third method, which is known to be actually used, is to react diethanolamine and 3-chloroaniline (see section 3.8 (iii) below). The remaining two isomers of CPP (pCPP and oCPP) could be made in a similar way.

It is important to remember that the above-mentioned precursors are relatively simple chemicals which are widely available from chemical suppliers worldwide.

(ii) The mode and scope of the established or expected use of the new substance

Over the last year, in the majority of the Member States, mCPP-containing tablets, often designed to look like ecstasy, have increasingly been found in the context of various recreational activities (open-air dance/music festivals, dance clubs, rave scenes, street

([13]) Handling of the substances included in Table A is an exclusive right of the state.
([14]) Under section 1 of the decision on the medicinal products list, the substances listed in the Annex 1 to the decision (1024/2003) are medicinal products.

parades, etc.), where they are almost always sold/bought as the popular drug ecstasy. However, currently there seems to be no specific demand or market for mCPP in the EU.

Given the physical forms in which mCPP is available and the intended users, in the great majority of the cases the substance is taken orally (ingested). However, since mCPP in powder form is also available, it cannot be excluded that the substance is also injected. So far, only two cases of mCPP injection have been reported by the French NFP, both involving users who usually inject ecstasy.

Probably because the vast majority of the mCPP-containing tablets have a rather distinctive appearance (off-white or beige with multicoloured flecks), quite a few street names for this 'new type of ecstasy' have rapidly gained in popularity. For example, in France, seven such samples have been bought in the street by SINTES under the name 'Arlequin'. The same 'typical' tablets are known in Belgium as 'regenboogies' or 'arc-en-ciel', in the Czech Republic as 'duhovka' (iris, rainbow or rainbow-tinted) and in Slovenia as 'Rainbow'. Furthermore, a German self-help group reported on its website that similar tablets have been found in some German regions (Cologne, Stuttgart, Berlin). In the Netherlands and Sweden mCPP-containing tablets are known as X4.

In France, the tablets collected were bought as 'ecstasy' or 'MDMA' (in six cases), 'artisanal ecstasy' (one case), 'mixed LSD–MDMA or ketamine-MDMA' (one case) and 'MDEA' (one case). In addition, the Versace logo tablet has appeared under the name of 'Méduse'.

Where reported, the price of mCPP-containing ecstasy tablets varies considerably over time and across the Member States. The French NFP reported that at the end of 2004 the price of a tablet in Bayonne, south-west France, was €15, whereas in Hungary in the last three months the price of a mCPP-containing tablet was €5 (i.e. a little more expensive than an 'ordinary' ecstasy tablet). In Lithuania, the price is reported to be €2.30 at wholesale and €3.20 at retail level. Very recent information from Slovenia mentions that the price is €6.25 per tablet. A 150-mg X4 tablet in Sweden is reportedly sold on the Internet for approximately €10 (99 SEK).

The availability of mCPP-containing tablets as perceived by the NFPs seems to vary between the countries from limited (Austria, Sweden) to widespread (the Netherlands), but is in general described as increasing (Lithuania, the Netherlands, Austria). In France it seems also to vary between regions. Most countries, however, do not report on the estimated availability of mCPP.

(iii) Other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks.

Besides the use of mCPP as a drug of abuse, there are at least two legitimate uses of mCPP – for neurochemical and psychiatric research and for the synthesis of trazodone and possibly several other related medicinal products.

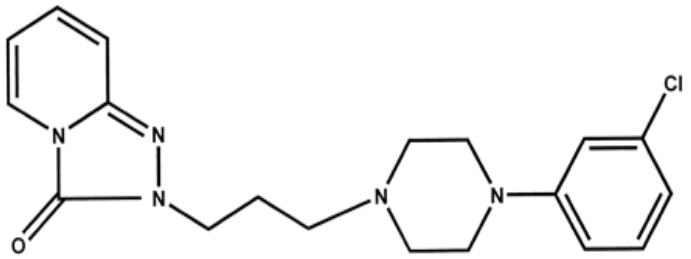
Research uses

Despite its non-specific pharmacology, mCPP has been used extensively in psychiatric research to test the sensitivity of the serotonin (5-HT) system of the brain. mCPP is of interest because it has 5-HT2C agonistic and 5-HT2A antagonistic properties as well as behavioural effects that are consistent with 5-HT agonistic properties such as anxiogenesis and anorexia in animals and humans.

CPP isomers have been extensively used for structure–activity relation research but there seems to be no real clinical application at present.

Trazodone – uses and synthesis

mCPP is well known as a metabolite of the triazolopyridine antidepressant medicine trazodone (recommended INN: 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazo-lo[4,3-a] pyridin-3(2H)-one hydrochloride). The molecular structure of trazodone is shown below.



trazodone

Trazodone (US patent no. 3,381,009 of 30 April 1968) is a prescription drug that is thought to act through combined 5-HT2 antagonism and 5-HT reuptake blockade (i.e. a selective serotonin reuptake inhibitor). It is often co-prescribed with other antidepressants as a sleep-inducing agent because of its sedative side-effects or as an augmentation strategy. Trazodone is used in the treatment of depression as well as aggressive behaviour, panic and anxiety disorders, alcoholism, cocaine withdrawal, etc.

Trazodone is extensively metabolised in the liver by hydroxylation, dealkylation, and N-oxidation. The active metabolite, mCPP, is formed by N-dealkylation of the piperazinyl nitrogen. It has been suggested that mCPP may contribute to the antidepressant efficacy of trazodone. However, according to limited users' reports on the Internet, trazodone is said to have no 'recreational value'.

Trazodone is registered in a number of Member States, e.g. as Trazolan® in Belgium, as Thombran® and Tombran® in Germany, as Pragmarel® and Pragmazone® in France, as Trittico® in Austria, the Czech Republic, Italy and Slovakia, as Tramensan® and Azona® in Finland; Desyrel® in Italy and as Molipaxin® in the UK (a non-exhaustive list).

Twelve Member States (the Czech Republic, Denmark, Finland, France, Hungary, Ireland, Italy, Portugal, Slovakia, Sweden, the Netherlands and the UK) that replied to the EMEA's request said that no spontaneously reported ADRs (relating to the terms misuse or abuse) had occurred in association with the use of trazodone.

However, according to information provided to the EMCDDA by the French NFP, the marketing authorisation of Pragmarel® was suspended in 1996, while Trazolam®, a Belgian medicine, has, since 2000, been granted only temporary authorisation (autorisation temporaire de traitement – ATU) because of indications that it causes behavioural disorders linked to central nervous system (CNS) degenerative changes.

A medicinal product related to Trazodone is nefazodone (Serzone®) (US patent no. 4,338,317 of 6 July 1982). Furthermore, a structure search of all substances in the Merck Index (12th edition) containing a chlorophenylpiperazine core shows that, apart from trazodone and nefazodone, there are at least two more medicinal products that are likely to be metabolised to mCPP: etoperidone (US patent no. 3,857,845 of 31 December 1974) and mepiprazole (US patent no. 3,491,097 of 20 January 1970). Both tranquillisers are known to have been used in Spain and epoperidone has been used in Italy.

Of the four medicinal products mentioned above, several synthetic routes to the target/active substance are theoretically possible, but for all of them mCPP is a possible starting product.

In accordance with Article 7.3 of the Decision, the EMEA, after consultation with the EMCDDA, requested information from the quality assessment teams of the Member States' NCA responsible for medicinal products about the use of mCPP as a reagent/intermediate in the synthesis of the four active substances mentioned above. The questions were addressed to both human and veterinary agencies. By 21 October, 13 responses from veterinary

agencies had been received (Denmark, Germany, Estonia, France, Greece, Ireland, Lithuania, Austria, Portugal, Slovenia, Spain, Sweden and the UK) and eight responses from human agencies (six Member States – Cyprus, the Czech Republic, Latvia, Lithuania, Malta, Slovenia and the UK – and Norway)

All responses from veterinary agencies were negative since none of the four products is authorised for veterinary use. As concerns the human medicinal products, three Member States – the United Kingdom, the Czech Republic and Lithuania – answered positively, i.e. mCPP is used to manufacture one of the four products, namely trazodone/Molipaxin in the UK and Trittico in the Czech Republic and Lithuania. mCPP is used either as a starting or as an intermediate material for synthesis of the active substance. In the Czech case, the producer of the active substance is based in Italy. It is reported that the manufacturer either synthesises mCPP from diethanolamine and 3-chloroaniline or is supplied by an external supplier (not specified).

4. Information from the EMEA as requested by Article 5.3 of the Decision

(a) Marketing authorisation

Twelve Member States (the Czech Republic, Denmark, Finland, France, Hungary, Ireland, Italy, the Netherlands, Portugal, Slovakia, Sweden and the UK) which replied to the EMEA's question reported that the new psychoactive substance mCPP has not obtained a marketing authorisation.

(b) Application for a marketing authorisation

Twelve Member States (the Czech Republic, Denmark, Finland, France, Hungary, Ireland, Italy, the Netherlands, Portugal, Slovakia, Sweden and the UK) which answered the EMEA's question reported that the new psychoactive substance mCPP is not the subject of an application for a marketing authorisation.

(c) Suspended marketing authorisation

Twelve Member States (the Czech Republic, Denmark, Finland, France, Hungary, Ireland, Italy, the Netherlands, Portugal, Slovakia, Sweden, and the UK) which answered the EMEA's question reported that there have been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance mCPP.

5. Conclusions

1. Over the last year, in the majority of the Member States, mCPP-containing tablets, often designed to look like ecstasy, have increasingly been found in the context of various recreational activities, where they are almost always sold/bought as the popular drug ecstasy.

2. Eighteen Member States and one Third State reported single seizures of mCPP tablets, ranging from one to 25 300. One Member State reported a total of 81 040 tablets in 12 seizures.

3. In comparison with the seizures of illicit synthetic drugs, in particular amphetamine and ecstasy, the level of mCPP seized in the Member States is currently low. However the size of several single seizures clearly points to the involvement of organised crime in the trafficking, wholesale and distribution of mCPP.

4. Three Member States reported data indicating the involvement of organised crime in the acquisition, tabletting and/or trafficking of mCPP, with a tabletting unit discovered in one Member State.

5. There seems to be little evidence about significant public health or social risks. No fatality due to or involving mCPP has ever been reported. Two Member States reported intoxications involving mCPP.

6. At present there seems to be no specific demand or market for mCPP in the Member States. From the current stage of the knowledge of pharmacology of mCPP it would seem an unlikely substance to be used for recreational purposes in its own right.

7. One Member State controls 1-(3-chlorophenyl)piperazine as an illicit substance (i.e. under the terms of the UN drug control conventions) and one Member State controls mCPP as a medicinal product.

8. 1-(3-Chlorophenyl)piperazine is currently not under assessment and has not been under assessment by the UN system.

9. There is no marketing authorisation (existing, ongoing or suspended) for 1-(3-chlorophenyl)piperazine in the EU or in the Member States which responded to the EMEA. Furthermore, no adverse drug reactions (for abuse) to trazodone have ever been reported.

10. 1-(3-Chlorophenyl)piperazine is used to manufacture a medicinal product (trazodone) in at least three Member States.

6. Recommendations

1. In view of the fact that 1-(3-chlorophenyl)piperazine is confirmed to be used in the manufacture of at least one medicinal product (trazodone), the Council and the Commission should consider the procedure set out in Article 7.3 of the Decision, which stipulates that 'No risk assessment shall be carried out on a new psychoactive substance if: (a) the new psychoactive substance is used to manufacture a medicinal product which has been granted a marketing authorisation'. Furthermore, the Decision requires that where the new psychoactive substance falls into this category, 'the Commission, on the basis of data collected by the EMCDDA and Europol, shall assess with the EMEA the need for further action, in close cooperation with the EMCDDA and in accordance with the mandate and procedures of the EMEA'.

2. Although there is little evidence of significant public health or social risks, these could be thoroughly examined only through a scientific risk assessment taking into account the principles of proportionality and precaution. Should it be decided that a risk assessment on 1-(3-chlorophenyl)piperazine is an appropriate action, then consideration should be given to including the other two CPP isomers {1-(4-chlorophenyl)piperazine and 1-(2-chlorophenyl)piperazine} in the scientific review.