

1-(3-chlorophenyl)piperazine (mCPP)

Pre-Review Report

Expert Committee on Drug Dependence
Thirty-fifth Meeting
Hammamet, Tunisia, 4-8 June 2012



**World Health
Organization**

Acknowledgements

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Medicines Access and Rational Use Unit. The WHO Secretariat would like to thank the following people for their contribution in producing this pre-review report: Dr Simon Elliott, United Kingdom (literature review and drafting), Dr Caroline Bodenschatz (editing) and Mr Kamber Celebi, France (questionnaire report).

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Summary

1-(3-chlorophenyl)piperazine (mCPP) is a piperazine derivative with stimulant (including euphoric) and hallucinogenic properties. mCPP has never been licensed as a medicine but is a known metabolite of some anti-depressants (trazodone, nefazodone, enziprazole and etoperidone) and a tranquillizer (mepiprazole). Abuse was first reported in the mid-2000s across Europe but has since been reported in various other countries (e.g. USA). The mode of abuse is similar to that of “Ecstasy” with many users seeking MDMA-like effects, particularly with concomitant 1-benzylpiperazine (BZP), 1-(3-trifluoromethylphenyl)piperazine (TFMPP) and/or 1-(4-methoxyphenyl)piperazine (MeOPP) use. mCPP can be sold as “legal Ecstasy” or as a “legal high” or as “Ecstasy” itself. Such products can contain other piperazine derivatives but not in all cases. Very few user reports involve solely mCPP; of these, toxic effects reported include: nausea, hallucinations, headache and most frequently, anxiety. There are no published non-fatal or fatal hospital admissions. In Europe, a few cases reported to monitoring centres have mentioned hot flushes, some respiratory problems and coma but these all also involved other substances (unspecified). No specific studies have been performed to determine the abuse or dependence potential of mCPP but in animal discrimination studies, it has been found to mimic TFMPP, ethanol and 3,4-methylenedioxymethylamphetamine (MDMA) but not lysergic acid diethylamide (LSD). Its abuse and dependence potential in humans is unclear.

Pre-review of 1-(3-chlorophenyl)piperazine (mCPP)

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

6640-24-0 (free base)

65369-76-8 (dihydrochloride salt)

C. Other Names

1-(3-chlorophenyl)piperazine, 3-CPP, 3Cl-PP, meta-chlorophenylpiperazine, mCPP. These abbreviations should be treated with caution since the term 'CPP' is also used for the unrelated herbicide 2-(4-chlorophenoxy)propionic acid.

D. Trade Names

None. (Please refer to section 11 of this document)

E. Street Names

mCPP has been associated with various street names including "X4", "Arlequin", "Regenboogies", "Arc-en-ciel", "Duhovka", "Rainbow" and "Smarties". mCPP has also been found in "Ecstasy" tablets stamped with a variety of logos.

One should be aware of the fact that street names are not always exclusive for just one substance.

F. Physical properties

mCPP is a white power. It is available as a monohydrochloride (white powder) or as a dihydrochloride salt. Liquid mCPP is also available.

G. WHO Review History

Several reports suggest misuse of mCPP over the last years. At the time being, neither BZP nor any other substituted piperazine is listed in the Schedules of the United Nations 1971 Convention on Psychotropic Substances. In order to bring more conclusive scientific evidence on the overall risks of mCPP for an eventual international scheduling, the WHO Secretariat has decided to initiate at the 35th ECDD a pre-review.

2. Chemistry

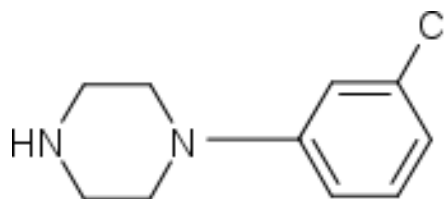
A. Chemical Name

IUPAC Name: 1-(3-chlorophenyl)piperazine

CA Index Name: 1-(3-chlorophenyl)piperazine

B. Chemical Structure

Free base:



Molecular Formula: C₁₀H₁₃ClN₂

Molecular Weight: 196.68 (free base)

233.14 g/mol (dihydrochloride salt)

Melting point: n/a (free base)

210-214 °C (dihydrochloride salt)

Boiling point: n/a

Fusion point: n/a

C. Stereoisomers

mCPP has no chiral centres and therefore no stereoisomers. There are two positional isomers of mCPP, namely 1-(4-chlorophenyl)piperazine (also known as pCPP, para-CPP, 4CPP and 4Cl-PP) and 1-(2-chlorophenyl) piperazine, (also known as oCPP, ortho-CPP, 2CPP and 2Cl-PP). Both are commercially available, but abuse is solely attributed to 3-CPP.

D. Synthesis

mCPP is an entirely synthetic compound and is available from retail chemical suppliers (e.g. Sigma-Aldrich). Because of this, illicit synthesis may not be necessary, however, processes may involve piperazine with *m*-dichlorobenzene; *m*-chloroaniline with bis(2-chloroethyl)amine; or diethanolamine with 3-chloroaniline (EMCDDA drug database).

E. Chemical description

mCPP is an aryl-substituted piperazine.

F. Chemical properties

No data.

G. Chemical identification

Methods for the identification of mCPP have been provided by Wohlfarth et al. (2010) and Moreno et al. (2012).

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

4.1. Pharmacodynamics

Neuropharmacology and effects on central nervous system:

Numerous *in vitro* and animal studies have been performed using mCPP. Overall, studies have demonstrated that mCPP affects all monoamine systems but particularly serotonergic pathways. Although studies have evolved and previous results have been re-evaluated, mCPP appears to have both antagonistic and agonistic activity at 5-HT₂ and 5-HT₁ receptor sites with additional binding at 5-HT₃ receptors (Murphy *et al.*, 1991; Zajdel *et al.*, 2007). Furthermore, as for TFMPP and MDMA, mCPP has been shown to produce stimulation of SERT-mediated release of endogenous 5-HT from neurons (Pettibone and Williams, 1984). For the other neurotransmitter systems, mCPP exhibits affinity for α_2 -adrenoreceptor sites (Smith and Suckow, 1985) with little affinity for D₁ and D₂ dopamine receptors in human brain (Hamik and Peroutka, 1989). Uptake inhibition of serotonin and noradrenaline has also been demonstrated in studies with rats (Fuller *et al.*, 1981 and Garattini *et al.*, 1976). mCPP was shown to have antinociceptive effects in squirrel monkeys and rats (McKearney, 1989 and Rochat *et al.*, 1982). However, in humans, no analgesic effect was reported in patients suffering chronic pain (Kishore-Kumar *et al.*, 1989).

Human studies found that the administration of mCPP (oral or intravenous) caused increases in body temperature and increases in anxiety and euphoria. In rats, hyperthermia was found to be dose-dependent (Gudelsky *et al.*, 1986) but this relation with dose has not been demonstrated in humans (Schwartz *et al.*, 1995). Increases in behavioural responses (e.g. anxiety, euphoria, depression) were less pronounced in older subjects (mean age: 62-years-old) compared to younger subjects (mean age: 32 years old) and were exaggerated if mCPP was administered at night (Lawlor *et al.*, 1989a and Lawlor *et al.*, 1991). Additional physical symptoms noted in experiments included nausea, dizziness and sweating – particularly at high oral doses (0.5 mg/kg) (Murphy *et al.*, 1991). Sleep studies indicated a mCPP-induced reduction in total, REM and slow-wave sleep, compared to a placebo (Lawlor *et al.*, 1991). Increases in prolactin and cortisol concentrations have been demonstrated in numerous animal and human studies and may relate to the physiological and psychological effects seen (Ghaziuddin *et al.*, 2003; Murphy *et al.*, 1991). In humans, a gender difference was noted, with females producing higher concentrations of prolactin and cortisol but this did not significantly affect the side effects observed (Ghaziuddin *et al.*, 2003).

Effects on cardiovascular, respiratory, gastrointestinal, liver, kidneys and genitourinary systems

Animal and human studies showed mCPP caused an increase in blood pressure and heart rate, thought to be due to initial and delayed vasoconstriction (Bagdy et al., 1989; Ghaziuddin et al., 2003). In rats, a reduction in food intake and body weight gain was observed (Vickers et al., 2000). With regard the genitourinary system, although mCPP administration resulted in penile erections in rats and monkeys, such effects were not observed in humans (Murphy et al., 1991).

Behavioural studies in animals

Numerous animal studies have been performed. In summary, mCPP produced a dose-dependent reduction in spontaneous ambulatory and basal locomotor activity (Murphy et al., 1991). Other behavioural effects related to serotonergic agents (e.g. head twitches, shaking) were noted in additional studies (Kennett and Curzon 1988). Increased grooming and chewing activity was seen in rodents (Kirstein and Spear 1988; Stewart et al., 1989). Tests of social interaction indicated a potential anxiogenic effect (Kennett et al., 1989) and mCPP did not exhibit anti-depressant effects in forced swim tests (Cryan and Lucki, 2000). In many of the animal models, mCPP appeared to have comparative activity to TFMPP (Murphy et al., 1991).

Effects in humans

A variety of studies have been performed involving humans, with a range of population types. mCPP is also the most extensively used probe of serotonin function in psychiatry (Kahn and Wetzler et al., 1991). In healthy subjects, oral and intravenous administration of mCPP have been shown to increase body temperature, blood pressure and heart rate, cause anxiety, euphoria, nausea, dizziness, headaches, sweating and reduced sleep. Overall, effects were dose-dependent and appeared greater with intravenous administration (Murphy et al., 1991). mCPP has also been administered to patients with neuropsychiatric disorders (i.e. panic disorder, obsessive-compulsive disorder (OCD), depression, Alzheimer's disease, alcoholism/substance abuse and bulimia). Both neuroendocrine and behavioural differences were observed when compared to control volunteers. mCPP produced increased anxiety, hostility (Kahn et al., 1988), an exacerbation of OCD (Hollander et al., 1988), euphoria (Jacobsen et al., 1994), perceptual changes (Lawlor et al., 1989b) and agitation in schizophrenics (Koreen et al., 1997). In a study of MDMA users where MDMA and mCPP were administered separately to MDMA users, mCPP did not affect heart rate and blood pressure (unlike administered MDMA). However, of the subjective effects, mCPP produced similar stimulant and hallucinogenic effects (Tancer and Johanson, 2001).

Interactions with other substances and medicines

Based on the pharmacology of mCPP, it is expected that an interaction with other substances that affect the monoamine systems might occur. In particular, other serotonin-releasing agents and re-uptake inhibitors are likely to exacerbate the effects of mCPP and vice versa. In the case of serotonergic compounds (e.g. most anti-depressants and MDMA), the development of a serotonin syndrome is possible. Concomitant administration of anti-depressants (e.g. clomipramine and fluoxetine) has been shown to exacerbate the effects of mCPP in humans (Murphy et al., 1991). Particular toxicity issues may arise if trazodone or nefazodone is ingested as mCPP is a known metabolite of these anti-depressants. Self-reporting users indicate poly-substance use is common (e.g. GHB/GBL) and many mention the additional use of other piperazines (especially

BZP and TFMPP). With comparable pharmacology, poly-piperazine use could also result in adverse effects, supported by some user reports that mention nausea and headache (Erowid and The Lycaeum).

4.2. Routes of Administration

As mCPP is typically obtained in the form of a powder, tablet, capsule or liquid, the primary route of administration is oral consumption. However, insufflation (“snorting”) has been mentioned in self-reports on the Internet (Erowid). Intravenous use is also a possibility (as for amfetamines) but such a practice is rare. In a UK study, out of 26 tablets/capsules analysed as part of voluntarily amnesty bin submissions, only 1 tablet contained mCPP together with BZP and TFMPP (Kenyon et al., 2007). As for the other substituted piperazines, user reports and seizure data indicate doses for mCPP to be typically between 10-200 mg (Erowid, The Lycaeum; EMCDDA Early Warning System reports).

4.3. Pharmacokinetics

mCPP is a metabolite of the anti-depressant medicines trazodone, nefazodone, enziprazole and etoperidone and of the minor tranquillizer mepiprazole (Fong et al., 1982; Rotzinger et al., 1998; de Boer et al., 2001; Yan et al., 2002; Staack and Maurer, 2003). This has been found in both animal and human studies. mCPP is formed by dealkylation of these via the CYP 3A4 isoform of the cytochrome P450 enzyme (Kalgutkar et al., 2005). A number of human studies have been performed involving administration of mCPP directly. The major metabolite of mCPP was found to be *p*-OH-mCPP (*para*-hydroxy-mCPP) via CYP2D6 mediated hydroxylation (Rotzinger et al., 1998; Maurer et al., 2004). Due to the involvement of cytochrome P450 in the metabolism of precursor substances and mCPP itself, the co-ingestion of these as well as genetic polymorphisms and drug inducers or inhibitors could affect the metabolism and plasma concentration of mCPP and its metabolites. For example, co-administration of fluoxetine was found to produce a 4-fold increase in mCPP plasma concentrations (Hollander et al., 1991).

In humans, Feuchtl et al. found that maximum mCPP concentrations varied 2.3-fold after intravenous infusion and 8-fold after oral administration (Feuchtl et al., 2004). The absolute bioavailability ranged from 12% to 84% with an elimination half-life ranging from 2.4 h to 6.8 h after intravenous infusion and from 2.6 h to 6.1 h after oral administration. However, the authors stated that the kinetic data as well as the pharmacodynamic response varied to an extent that precluded pharmacokinetic-pharmacodynamic modelling. The wide inter-individual variability in its disposition kinetics could not be fully explained by genetic variation of the mCPP-metabolizing CYP2D6 enzyme (Feuchtl et al., 2004). In a previous study, eight female and six male healthy volunteers were included in a randomized, double-blind, double-dummy, three-way crossover design of single-dose intravenous (0.1 mg/kg), oral (0.5 mg/kg), and placebo treatment, with 24-hour follow-up. mCPP showed a large variability in clearance (11-92 mL/hr) and bioavailability (14-108%) (Gijssman et al., 1998).

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of mCPP. Despite being a serotonergic compound, mCPP has not been found to have a neurotoxic potential, unlike some amphetamine-derivatives (e.g. MDMA and *p*-chloroamphetamine) which appears related to its neuronal mode of action (Gobbi et al., 2002).

6. Adverse reactions in humans

Overall, user reports and study information indicates that mCPP produces stimulant, anxiety and hallucinogenic effects. Additional adverse effects include nausea, headache, dizziness, sweating and potential cardiovascular symptoms (e.g. increased heart rate and blood pressure); although the latter effects are not exhibited in some studies (Tancer and Johanson, 2001). Despite the relatively high number of human studies involving mCPP administration, there are a very limited number of user reports even on the Internet. (Erowid and The Lycaeum). The human study data invariably involve mCPP alone, whilst the limited user reports generally mention the use of other substances of abuse. This introduces the possibility of drug-drug interactions or exacerbation of toxic effects for poly-substance users. Abridged versions of these reports are as follows:

(i) Dec 2006 (USA?) – 120 mg mCPP in a capsule. Effects noted after 45 minutes post-dose. “a grand euphoria, not quite on the level of, say, MDMA, but it was markedly close. I was getting powerful color enhancement, but no fractal imagery like with mushrooms or stronger psychedelics.” “At this relatively high dose the MDMA comparisons tend to be drowned out by the more significant psychedelic effects,....like a light dose of LSD or mushrooms but with a different, more serotonergic body high....I'm used to taking around 30-50mg of mCPP, and at this dose, it felt more like a psychedelic than an ecstasy imitation.”

(ii) Dec 2006 (USA?) – approx. 300 mg mCPP as liquid. Effects noted after 1 hour post-dose. “I felt a strong numbing of face common to this chemical. Nausea rises quickly from here due to dose”. After a further hour the user experienced an elevated mood, very euphoric but anxious.

(iii) 1999 (unknown location) – 25 mg mCPP + 110 mg BZP + 60 mg TFMPP + GHB. Comments mention frequent nausea and physical tiredness within an hour of use. The user concluded it was “a powerful stimulant, which would have been ok were it not for the negative side effects”....As a replacement for MDMA it's a non starter. It has none of the warmth of MDMA, very little empathic quality, and is much more akin to speed [amphetamine] or dexys-only more coarse, harsh and physically draining”.

(iv) 2006 (unknown location) – 30 mg mCPP + 50 mg MeOPP. “After about an hour and a half, I felt a pretty decent euphoria that was not unlike an MDMA.” Following occasional lethargy, the user then took additional mCPP (30 mg) and MeOPP (50 mg) and reported similar effects to MDMA but with no jaw clenching, nausea and pupils remained normal. A further 15 mg of mCPP and MeOPP was insufflated producing an extreme burning sensation but “kicked in pretty fast and increased the effects, mostly the visual components.”

Cases of mCPP intoxication in humans

Cases of non-fatal intoxication were reported in some users at a specific music festival. Users complained of hot flushes, feelings of suffocation, with some injecting users these effects in addition to breathing difficulties were reported by the French National Focal Point (Europol-EMCDDA report 2005). At the same festival, two users went into a coma following mCPP use but other substances (not specified) were also involved (Belgium National Focal Point). No published intoxications have appeared in the literature.

There have been no reports of fatal intoxication where mCPP has been detected. However, a major problem in investigating the involvement of mCPP in hospital admissions and fatalities is the potential lack of laboratory confirmation or diagnosis. Although various methods have been published (Peters et al., 2003; Staack and Maurer, 2003), mCPP is not always included in routine or targeted toxicological analysis or may be detected but not identified as being mCPP.

7. Dependence potential

Although mCPP has been used in the study of dependence of other substances (e.g. cocaine and opiates), there have been no specific studies concerning the dependence potential of mCPP itself. However, in discrimination studies in animals, mCPP was found to mimic TFMPP, ethanol and MDMA but not LSD (Cunningham and Appel, 1986; Gatch, 2005; Cunningham and Appel, 1987; Johanson et al., 2006). As described elsewhere, human administration studies and user reports seem to support this but the dependence potential of mCPP remains unclear.

Based on the recent data available it seems that mCPP (like MDMA) has limited dependence producing potential (Annex 1).

8. Abuse potential

There have been no specific studies concerning the abuse potential of mCPP. However, in discrimination studies in animals, mCPP was found to mimic TFMPP, ethanol and MDMA but not LSD (Cunningham and Appel, 1986; Gatch, 2005; Cunningham and Appel, 1987; Johanson et al., 2006). As described elsewhere, human administration studies and user reports seem to support this but the abuse potential of mCPP remains unclear.

9. Therapeutic applications, extent of therapeutic use and epidemiology of medical use

Although mCPP is a metabolite of the anti-depressants trazodone, nefazodone, enziprazole, etoperidone and of the minor tranquillizer mepiprazole (see Section 3), it has been directly used in psychiatry to study the involvement of serotonin (Kahn and Wetzler, 1991). However, mCPP itself is not, and has not been, the subject of a marketing authorisation.

10. Listing on the WHO Model List of Essential Medicines

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

11. Marketing authorizations (as a medicine)

Based on the report of the WHO questionnaire for review of psychoactive substances for the 35th ECDD, (Annexe 1) only Iraq authorized mCPP as a medical or veterinary product of the 60 countries that responded. Although mCPP has not been granted for market admission Iraq indicated that the dosage for tablets is 150 mg and indicated that the dosage for capsules is 50 mg and 100 mg. The registered indication is antidepressant.

12. Industrial use

mCPP has no industrial use.

13. Non-medical use, abuse and dependence

The report of the WHO questionnaire for review of psychoactive substances for the 35th ECDD, (Annexe 1) indicate that 9 countries reported that mCPP is used in a harmful way, 12 countries reported that it is not used in a harmful way and in 16 countries this is unknown. When abused, mCPP is mostly administered orally and it is also, snorted or injected.

Only the USA reported other legitimate use of the substance as a serotonin receptor agonist in research.

mCPP use and seized material has been reported in various countries including USA and many in Europe (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Romania, Spain, Slovakia, Sweden, UK).

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

As for BZP and TFMPP, mCPP use appears to be associated with situations similar to that of “Ecstasy”, or with users who are seeking effects similar to “Ecstasy” (MDMA in particular). Therefore instances of misuse, abuse and dependence would be limited to such individuals rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other piperazine-derivatives (e.g. BZP, TFMPP, MeOPP) or other substances. Although some discrete cases of non-fatal intoxication have been reported in Europe, these few cases did not involve solely mCPP. No fatal or other non-fatal intoxications have been reported.

It seems that there is only a limited demand from users for mCPP. For many, it compares unfavourably to MDMA. (Annexe 1)

15. Licit production, consumption and international trade

The report of the WHO questionnaire for review of psychoactive substances for the 35th ECDD, (Annexe 1) indicate that in Germany mCPP is used as an intermediate in the production of the active agent Trazodon and three related substances and it is commercially available from retail chemical suppliers. Brunei indicated that they import the substance. The USA indicated Sigma-Aldrich as a supplier.

16. Illicit manufacture and traffic and related information

the report of the WHO questionnaire for review of psychoactive substances for the 35th ECDD, (Annexe 1) No specific data.

17. Current international controls and their impact

No current international controls under any of the international drug control conventions.

18. Current and past national controls

See also report on the WHO questionnaire for review of psychoactive substances for the 35th ECDD in Annex 1. Eight countries reported that mCPP is controlled under legislation that is intended to regulate availability of substances of abuse. Denmark has added it to the list of controlled substances in the Executive Order on euphoria Substances. In Germany mCPP was included in the list of tradable but not prescribable narcotic substances and it is subject to the Narcotics Act in Germany without time limit.

European Union: not widely controlled at present (March 2007), except for: Belgium, Denmark, Germany, Greece, Hungary, Lithuania, Malta and Slovakia.

New Zealand: to be controlled

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

No data.

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ANNEX 1:WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD: 1-(3-chlorophenyl)piperazine (mCPP)

The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for 1-(3-chlorophenyl)piperazine (mCPP) by 60 countries.

LEGITIMATE USE

Of the responded countries one country, Iraq, authorized mCPP as a medical or veterinary product. Although mCPP has not been granted for market admission Iraq indicated that the dosage for tablets is 150 mg and indicated that the dosage for capsules is 50 mg and 100 mg. The registered indication is antidepressant.

There are no countries that legitimated mCPP for technical use. Only the USA reported other legitimate use of the substance and use mCPP as a serotonin receptor agonist in research.

Brunei indicated that they import the substance. Germany indicated that it is commercially available from retail chemical suppliers and the USA indicated Sigma-Aldrich as a supplier.

ABUSE

9 countries reported that mCPP is used in a harmful way, 12 countries reported that it is not used in a harmful way and in 16 countries this is unknown.

When abused, mCPP is mostly administered orally and it is also, snorted or injected. 4 countries indicated tablets as the most common way how the substance is abused. Germany reported also, although less common, the abuse in the form of capsules and loose powder.

Of the 9 countries reporting, on the use of mCPP in a harmful way, 3 countries reported on the extent of the harmful use. Two countries reported on the extent of public health or social problems associated with the harmful use of mCPP.

In Germany mCPP is used as an intermediate in the production of the active agent Trazodon and three related substances. mCPP may show weak stimulant and hallucinogenic effects, but several side effects are reported. In illicit preparations mCPP is sometimes mixed with other piperazines (e. g. TFMPP) or other substances (e. g. MDMA). It seems that there is only a limited demand from users for mCPP. For many, it compares unfavourably to MDMA.

The negative effects of mCPP include anxiety, dizziness, confusion, shivering, sensitivity to light and noise, fear of losing control, migraine and panic attacks. According to the Europol-EMCDDA Active Monitoring Report on mCPP no serious intoxications or fatal cases related to mCPP have been reported in the European Union until 2007. There is little evidence that it is a particularly dangerous substance in terms of acute toxicity. However, the chronic (prolonged use) toxicity has not been established. Based on the data available it seems that mCPP (like MDMA) has limited dependence producing potential.

Thailand reported that there is no concrete evidence about the use of this substance and reported on the extent of public health or social problems associated with the harmful use of mCPP.

CONTROL

8 countries reported that mCPP is controlled under legislation that is intended to regulate availability of substances of abuse.

Denmark has added it to the list of controlled substances in the Executive Order on euphoria Substances.

In Germany mCPP was included in the list of tradable but not prescribable narcotic substances and it is subject to the Narcotics Act in Germany without time limit.

IMPACT OF SCHEDULING

The impact of scheduling is likely to be negligible considering the extremely limited legitimate use of this substance

Brand Name

No information

Form

- Tablet (Iraq)
- Capsule (Iraq)

Technical Use

The USA uses it as a serotonin receptor agonist in research.