

1-(3-trifluoromethylphenyl) piperazine (TFMPP) Pre-Review Report

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



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-trifluoromethylphenyl)piperazine (TFMPP) is a piperazine derivative with mild stimulant effects and hallucinogenic properties. TFMPP has never been licensed as a medicine but is a known metabolite of a previously used anti-inflammatory analgesic (antrafenine). Abuse was first reported in the late 1990s in the USA and Scandinavia along with BZP but has since been reported in various other countries (particularly New Zealand and in Europe). The mode of abuse is similar to that of “Ecstasy” (3,4-methylenedioxymethylamphetamine) with many users seeking MDMA-like effects, particularly with concomitant 1-benzylpiperazine (BZP) use. Many suppliers of TFMPP market the substance as “legal Ecstasy” or as a “legal high”. Such products typically contain other piperazine derivatives in variable quantities. Very few user reports involve solely TFMPP use, of these toxic effects reported include: nausea, hallucinations and slight tremors. Hospital admissions have occurred but all involved other substances (including piperazines). Although TFMPP has been found in fatalities, due to the manner of death and/or the presence of other substances, it is difficult to specifically determine the toxicological significance of TFMPP in these instances. Animal studies have indicated that TFMPP is unlikely to possess an abuse or dependence potential but there are no human clinical studies to support this.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not applicable.

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

15532-75-9 (free base)

C. *Other Names*

1-(3-trifluoromethylphenyl)piperazine, 3-TFMPP, Trifluoromethylphenylpiperazine, *m*-trifluoromethylphenylpiperazine, mTFMPP, *N*-(*p*-trifluoromethylphenyl)piperazine, *N*-(α,α,α -trifluoro-*m*-tolyl)piperazine.

D. *Trade Names*

Not applicable.

E. *Street Names*

TFMPP has been associated with various street names including “X4”, “Molly” and numerous brand names relating to its availability as a perceived legal “Ecstasy” alternative (e.g. “PEP”, “Twisted”, “Flying Angel” and “Wicked High”).

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

F. *Physical properties*

No data.

G. *WHO Review History*

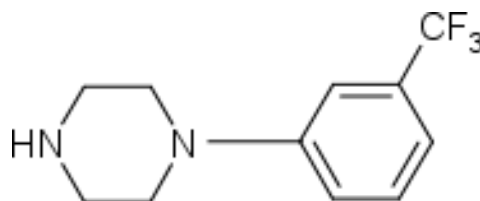
Several reports suggest misuse of TFMPP over the last years. At the time being, neither BZP nor any other substituted piperazine is listed in the Schedules of the United Nations 1971 Convention on Psychotropic Substances. In order to bring more conclusive scientific evidence on the overall risks of TFMPP 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-(Trifluoromethyl)phenyl)piperazine

CA Index Name: 1-(3-(Trifluoromethyl)phenyl)piperazine

B. Chemical Structure**Free base:**

Molecular Formula:	C ₁₁ H ₁₃ F ₃ N ₂ (free base)
Molecular Weight:	230.23 g/mol (free base)
Melting point:	n/a
Boiling point:	n/a
Fusion point:	n/a

C. Stereoisomers

TFMPP has no chiral centres and therefore no stereoisomers. Positional isomers of the trifluoromethyl moiety such as 4-TFMPP exist and are available but abuse is solely attributed to 3-TFMPP.

D. Synthesis

TFMPP is an entirely synthetic compound and is available from retail chemical suppliers. Specific information is not available but chemical synthesis is likely to involve piperazine monohydrochloride or dihydrochloride (as per BZP).

E. Chemical description

No data.

F. Chemical properties

No data.

G. Chemical identification

Methods for the identification and quantification of 3-TFMPP in body fluids have been provided by Peters et al. (2003), Tsutsumi et al. (2005), Elliott and Smith (2008), Antia et al. (2010) and Wohlfarth et al. (2010). Most of these rely either on gas chromatography with mass spectrometry (GCMS) or liquid chromatography coupled with mass spectrometry (LC-MS).

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

4.1. Pharmacodynamics

Neuropharmacology and effects on central nervous system

Studies have demonstrated that TFMPP is a non-selective serotonin (5-HT) receptor agonist—5-HT₁ and 5-HT₂ subtypes (Fuller, 1988; Hoyer, 1988; Berg *et al.*, 1998; Glennon *et al.*, 1988; Herndon *et al.*, 1992 and Schechter, 1988). TFMPP also exhibits presynaptic action that is similar to MDMA (but 3-fold less potent), such as *in vitro* and *in vivo* stimulation of SERT-mediated release of endogenous 5-HT from neurons (Pettibone and Williams, 1984; Auerbach *et al.*, 1991 and Baumann *et al.*, 2005). In addition, animal studies have demonstrated that TFMPP is a selective releaser of 5-HT transporter substrate (³H]5-HT) and increased extracellular 5-HT concentration (Baumann *et al.*, 2004; Baumann *et al.*, 2005). Administration of BZP and TFMPP at a 3 mg/kg dose (1:1 ratio) produced parallel increases in 5-HT and dopamine (DA), mirroring the results obtained with MDMA. A higher dose of 10 mg/kg BZP:TFMPP (1:1) increased DA to a higher degree than the substances alone, with some rats developing seizures - but may be more related to BZP than TFMPP. This suggested a synergistic activity of BZP and TFMPP, mimicking the effects of MDMA at a molecular level, but with a lower potency (Baumann *et al.*, 2004; Baumann *et al.*, 2005).

Interestingly, rather than BZP-induced hyperthermia, hypothermia was noted with TFMPP in mice (Maj *et al.*, 1988).

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

There are no published data. No specific effects were noted in animal studies.

Behavioural studies in animals

In rats, unlike BZP, TFMPP did not exhibit locomotor stimulant effects such as ambulation (circling, sniffing, rearing) or stereotypy (head-bobbing, repetitive sniffing). However, when administered with BZP at high doses (10 mg/kg), these amphetamine-like effects were noted (Baumann *et al.*, 2004; Baumann *et al.*, 2005). In mice studies involving TFMPP, 1-(3-methoxybenzyl)piperazine (*m*-MeO-BZP), BZP and *meta*-chlorophenylpiperazine (*m*-CPP), TFMPP was found to be the only compound active in the head twitch assay, eliciting a moderate head twitch response which was comparable to that previously observed with the MDMA enantiomers (Yarosh *et al.*, 2007). It was also reported that TFMPP had hallucinogenic effects (Yarosh *et al.*, 2007).

In rhesus monkeys, unlike BZP, TFMPP did not substitute for cocaine in self-administration studies or amphetamine discrimination studies (Fantegrossi *et al.*, 2005). When administered in combination with BZP, reinforcing effects were less than BZP alone with a TFMPP-induced dose-dependent reduction in response. At higher doses of TFMPP (1.0 mg/kg/inj), no overt signs of intoxication were noted but a disruption in behavioural activity was observed through suppression of a cocaine-mediated response. In amphetamine substance discrimination studies, a TFMPP dose of 17 mg/kg elicited a suppression of response rate, and ataxia and locomotor slowing were observed (Fantegrossi *et al.*, 2005). In another study in rats, TFMPP produced discriminative stimulus effects dissimilar to the hallucinogen DOM using a two-lever procedure (Glennon *et al.*, 1984).

Effects on cognition and behaviour in humans

No study data available.

Physiological effects in humans

In a randomised, double-blind, placebo-controlled study the subjective and physiological effects of BZP/TFMPP were investigated in 36 males (Lin et al., 2011). Participants were tested before and approximately 2 hours after administration of a single dose of placebo or 100/30 mg BZP/TFMPP. The results revealed that BZP/TFMPP increased blood pressure and heart rate and subjective rating scales revealed that BZP/TFMPP had dexamphetamine-like effects, increased dysphoria and feelings of self-confidence.

Another randomised, double-blind, placebo-controlled study in New Zealand involved volunteers who had previously used party pills containing BZP (Thompson et al., 2010). Participants received one of four treatments: a) 300 mg/74 mg BZP/TFMPP and placebo, b) 300 mg/74 mg BZP/TFMPP and 57.6 g alcohol, c) placebo and 57.6 g alcohol and d) double placebo. Driving performance effects and physiological effects (adverse events, cardiovascular effects, psychological function and delayed effects on sleep) were assessed. The study was stopped early, after 35 of the planned 64 subjects had undertaken testing, because of severe adverse events that occurred in 4 of 10 BZP/TFMPP-only subjects and 3 of 7 combined BZP/TFMPP and alcohol subjects. Severe events included agitation, anxiety, hallucinations, vomiting, insomnia and migraine. Such events did not occur with the 6 placebo subjects and 12 alcohol-only subjects. BZP/TFMPP also resulted in increased heart rate and blood pressure and in difficulty in getting to sleep. BZP/TFMPP was found to significantly improve the driving performance, decreasing standard deviation of lateral position (SDLP) at -4.2 cm. SDLP, the degree to which individuals adjust lane position, has been found to be very sensitive to the influence of sedative medicines and alcohol. The effect of alcohol was to increase SDLP: 2.3 cm. Overall, it was concluded that BZP/TFMPP alone or with alcohol carries a significant risk of severe adverse events at the assumed doses studied but the study design has been criticized (Antia et al., 2009).

Psychological effects in humans

There are few published human studies. Lin et al, indicated increased dysphoria and feelings of self-confidence in males (Lin et al., 2011). Self-reports from users on the Internet (Erowid and The Lycaeum) described a number of cognitive, mood and mental effects but many reports involve multiple substances in addition to TFMPP. There are a few reports with TFMPP taken alone, whereby users described TFMPP as a mild stimulant with slight mood elevation and some perceptual shift. As the majority of users appeared to take TFMPP in an attempt to mimic the effects of MDMA, many reports compare the effects with those of MDMA. Overall, although some entactogenic effects were noted, even with BZP, effects were not deemed to be comparable to MDMA. No users mentioned chronic effects. Given the basis of these reports it is difficult to make any definitive conclusions.

Interactions with other substances and medicines

Based on the pharmacology of TFMPP, 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

TFMPP and vice versa. In the case of serotonergic compounds (e.g. most anti-depressants and MDMA), the development of a serotonin syndrome may be possible. Self-reporting users indicate poly-substance use is common as an intended adjunct to TFMPP use and many mention the additional use of these substances (e.g. MDMA) as well as other piperazines (especially BZP and mCPP). Based on studies of BZP and TFMPP in rats, Baumann *et al.* (2004) suggested the potential for dangerous consequences (e.g. serotonergic syndrome) if the substances were taken in combination.

4.2. Routes of Administration

As TFMPP is typically obtained in the form of a powder, tablet or capsule, the primary route of administration is oral consumption. However, it does not preclude the possibility of the powder being "snorted" or smoked which have been noted for BZP and other piperazines in self-reports on the Internet (Erowid and The Lycaenum). Intravenous use is also a possibility (as for amphetamines) but such a practice is rare. In the New Zealand 'National household survey of legal party pill use' (Wilkins *et al.*, 2006), 98.8% of respondents ingested BZP/TFMPP. Although powders were commonly seen, only one individual (out of 2,010) claimed to have injected, two had snorted (insufflated), but none admitted to smoking the substance(s). The typical dose ingested by users appears to be between 50-200 mg of TFMPP (Wilkins *et al.*, 2006 and Erowid). In a UK study, 20 tablets/capsules contained between 28-133 mg of BZP (mean = 65 mg) and 4-72 mg of TFMPP (mean = 22 mg). The stated doses ranged between 105-200 mg BZP and 50-75 mg TFMPP (Kenyon *et al.*, 2007).

4.3. Pharmacokinetics

Animal studies

TFMPP is a metabolite of a previously marketed analgesic and anti-inflammatory medicine, antrafenine (Caccia *et al.*, 1985). Although antrafenine has been studied, direct pharmacokinetic data from animals are not available for TFMPP, in particular: absorption, distribution, AUC, C_{max}, T_{max} and half-life. However, in discrimination studies in rats, TFMPP was found to have an effective pharmacological dose (ED₅₀) of 0.17 mg/kg (Lyon *et al.*, 1986).

TFMPP appears to be metabolised by cytochrome P450 (involving the CYP2D6 isoenzyme and to a lesser extent, CYP1A2 and CYP3A4) (Staack *et al.*, 2004; Maurer *et al.*, 2004 and Tsutsumi *et al.*, 2005). This system is prone to genetic polymorphisms, so potential inter-individual and inter-species differences may occur and gender differences were noted in rats with female Dark Agouti rats producing higher TFMPP plasma levels than male rats (Staack *et al.*, 2004). However, overall, animal and human studies have noted the same major metabolite to be present: 4-hydroxy-TFMPP (4-OH-TFMPP or *p*-OH-TFMPP) which is also excreted as glucuronide and/or sulfate conjugates in urine (Staack *et al.*, 2004; Maurer *et al.*, 2004; Tsutsumi *et al.*, 2005). In rats receiving a single intraperitoneal 5 mg/kg dose of TFMPP, the cumulative amount of *p*-OH-TFMPP excreted within the first 48 hours reached approximately 64% of the dose, of which 70% was the glucuronide conjugated form. The cumulative amount of parent TFMPP excreted was less than 0.7% of the dose (Tsutsumi *et al.*, 2005).

Human studies

In humans, TFMPP may follow the same metabolic fate observed in rats. Staack *et al.* showed the involvement of cytochrome P450 (CYP2D6, CYP1A2 and CYP3A4 isoenzymes) during *in vitro* human liver microsomal studies (Staack *et al.*, 2004). It is proposed that as in the rat, *p*-OH-TFMPP is the major Phase I metabolite with glucuronide formation as the major Phase II product in humans (Staack *et al.*, 2004; Maurer *et al.*, 2004 and Tsutsumi *et al.*, 2005).

Human plasma concentrations of TFMPP were measured in blood samples taken from healthy adults (n = 6) over 24 hours following a 60-mg oral dose of TFMPP: these peaked at 24.10 µg/L (±1.8 µg/L) (C_{max}) after 90 minutes (T_{max}). Plasma concentrations of 1-(3-trifluoromethyl-4-hydroxyphenyl)piperazine peaked at 20.2 µg/L (±4.6 µg/L) after 90 minutes. TFMPP had two disposition phases (t_{1/2}) = 2.04 hours (±0.19 hours) and 5.95 hours (±1.63 hours). Apparent clearance (Cl/F) was 384 L/hour (±45 L/hour) (Antia *et al.*, 2010).

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of TFMPP.

6. Adverse reactions in humans

User reports and study information indicates that TFMPP appears to produce mild stimulant and hallucinogenic effects. TFMPP is commonly used in conjunction with BZP in order to seek the entactogenic effects of MDMA. Adverse effects are likely to occur when TFMPP is co-ingested with other substances (in particular MDMA and other serotonergic compounds) such as agitation, tachycardia and possibly seizures. Toxic effects with TFMPP alone have not been reported.

A New Zealand study of clinical admissions associated with party pill use (April-September 2005) reported that 61 patients attended the Emergency Department with adverse effects on 80 occasions (Gee *et al.*, 2005). The pills were purported to be BZP-based but the presence of additional piperazines cannot be discounted. Symptoms noted were anxiety, vomiting, headache, palpitations, confusion, collapse and seizures. However, only a small proportion of cases were confirmed by toxicological analysis (data not published) and the involvement of TFMPP was not confirmed in any of the cases.

In the New Zealand Household survey (Wilkins *et al.*, 2006), 2010 people aged between 13 and 45 years were questioned regarding their use of party pills. Physical problems reported were (in order of frequency) poor appetite, hot/cold flushes, heavy sweating, stomach pains/nausea, headaches and tremors/shakes. Psychological problems experienced were (in order) trouble sleeping, loss of energy, strange thoughts, mood swings, confusion and irritability. In this survey, one person in a hundred had visited an Emergency Department with 0.4% being admitted as a result of party pill use.

Although anecdotal and unpublished, a number of reports from users have been compiled on the internet. With concomitant use of BZP, only a few relate to TFMPP use alone and these are presented in brief below. It should also be noted that numerous

other reports include the combined use of other substances of abuse. Abridged versions of these reports are as follows:

(i) Jan 2001 (USA?) – 60 mg. Comments not mentioned until 8 hours post-dose. Pupils dilated with waves of some perceptual shift. “I think that a mood elevation was definitely one of the more primary effects. It was very subtle and mild in terms of visual trippiness”. “...effects of TFMPP...nothing like BZP except for the mood elevation. The CNS stimulation was barely evident and I think it probably was a side effect of the mood elevation and anticipation. There also is no parallel between the TFMPP and anything anywhere near MDMA. I would place it more like a small but perceivable amount of LSD, without the self conscious feeling and clenching”.

(ii) August 2000 (unknown location) – 100 mg as liquid. “Alert at 30min, peak after about an hour. Lasts for two or three hours, then decline”. “General impression was that of a mild, pleasant, mellow trippyness. Thoughts flowing freely...full control over everything at all times...Call it half a hit of LSD”. “Contrary to what I had read, there was no jaw-clenching...a light tremor in my hands was the only peripheral effect I could detect. I didn't even have dilated pupils”.

(iii) August 2000 (unknown location) – 100 mg TFMPP. Felt alert after 25 minutes, with effects peaking between 1-2.5 hours post dose which then faded. Very “unemotional” but some “trippy” effects experienced.

Of the reports that involve concomitant use of other substances, some mention adverse effects. As TFMPP is reported to be ingested in combination with BZP in particular (typically within the same product), reports involving these substances are therefore relevant.

(iv) April 2007 (UK?) – 100 mg BZP + unknown dose TFMPP. 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”.

(v) August 2000 (unknown location – same individual as (iii)) – 200 mg BZP + 100 mg TFMPP. Some muscle stiffness with nausea.

Cases of TFMPP intoxication in humans

There have been various reports of non-fatal and fatal intoxication where TFMPP has been found. However, a major problem in investigating the involvement of TFMPP in hospital admissions and fatalities is the potential lack of laboratory confirmation or diagnosis. Although various methods have been published (Peters *et al.*, 2003; de Boer *et al.*, 2001), TFMPP is not always included in routine or targeted toxicological analysis or may be detected but not identified as being TFMPP (Elliott, 2007).

Non-fatal cases

Between June 2006 and November 2007, TFMPP was detected in nine patients in the UK, with BZP also found in all cases (Elliott, 2007 and Elliott, 2011). The cases were

confirmed by toxicological analysis as summarised below. No blood samples were available.

Case 1: June 2006 – 32-year-old male; Urine BZP = 35.75 mg/l, 3-TFMPP = 0.40 mg/l. No clinical information.

Case 2: October 2006 – 15-year-old female; Urine BZP = 8.33 mg/l, 3-TFMPP = 0.48 mg/l. No clinical information.

Case 3: December 2006 – 26-year-old male; Urine BZP ~ 39.87 mg/l, 3-TFMPP ~ 12.13 mg/l. MDMA and methadone also present. He presented at an Accident and Emergency Department 12 hours after having taken 6 blue ‘legal high’ tablets. Symptoms included chest pains, visual hallucinations, dizziness, drowsiness and dilated pupils.

Case 4: December 2006 – 24-year-old male; Urine BZP ~ 20.86 mg/l, 3-TFMPP ~ 1.53 mg/l. MDMA, cocaine and quinine also present. No clinical information.

Case 5: July 2007 – 19-year-old male; Urine BZP = 202.70 mg/l, 3-TFMPP = 20.66 mg/l. MDMA and amphetamine also present. No clinical information.

Case 6: August 2007 – 24 year-old male; Plasma BZP = 0.32 mg/l, 3-TFMPP = 0.08 mg/l. 2 “BZP” tablets taken. Insufficient sample volume for additional drug analysis.

Case 7: August 2007 – 41 year-old female; Urine BZP = 5.21 mg/l, 3-TFMPP = 0.40 mg/l. MDMA, amphetamine, methadone and metoprolol also present. Critical care admission.

Case 8: November 2007 – age/sex not known; BZP and 3-TFMPP detected in the urine. Plasma BZP = 0.47 mg/l, 3-TFMPP = 0.10 mg/l. No other substance or clinical information available.

Case 9: November 2007 – 18-year-old male; BZP and 3-TFMPP detected in the urine. No other substance or clinical information available.

Fatal cases

There have been relatively few instances of fatalities involving TFMPP. 21 cases have been formally published from the UK (Elliott and Smith, 2008 and Elliott, 2011). None involved TFMPP alone.

Case 1: (August 2006) – A 26-year-old male driver was involved in a fatal road traffic accident. Subsequent information indicated he may have used “Wicked High” pills. Comprehensive toxicological analysis of post mortem blood and urine samples found a urinary BZP of 15.73 mg/l, TFMPP 1.04 mg/l, cannabis, cocaine, ephedrine, MDMA, ketamine and ethanol 128 mg/dl. The blood levels were: BZP 0.71 mg/l, TFMPP 0.05 mg/l, ketamine 0.96 mg/l and ethanol 77 mg/dl.

Case 2: (December 2006) – A 17-year-old male fell through the roof of a building having walked across it whilst taking a shortcut. He had been to a party and may have taken “Ecstasy” and drank alcohol. Comprehensive toxicological analysis of post

mortem blood and urine samples found a urinary BZP of 8.72 mg/l, TFMPP 0.92 mg/l and ethanol 248 mg/dl. The blood analysis showed BZP 1.39 mg/l, TFMPP 0.15 mg/l and ethanol 140 mg/dl.

Subsequently, BZP and 3-TFMPP were found in a further 19 fatalities between 2007-2010 (Elliott, 2011). Both substances were detected together in each case, suggesting possible concomitant ingestion. Of the cases, 6 involved a mechanical cause of death (e.g. RTA, hanging), 6 cases were likely due to other substance use (e.g. heroin, methadone) and 7 cases had no obvious alternative cause of death. However, due to the presence of other substances, medical history and case circumstances the actual significance of BZP or 3-TFMPP was unclear. In fact the highest post mortem blood 3-TFMPP concentration was only 0.30 mg/L, found where the manner of death was hanging. In all the cases, due to the toxicologically significant presence of other substances and/or alcohol, it is difficult to determine the role of TFMPP (and BZP when used in combination) in any potential impairment of driving ability or judgement and any effect on the individuals' state of mind. It is also not possible to relate any particular concentration of TFMPP to specific effects or outcome.

7. Dependence potential

There have been few studies regarding the dependence potential of TFMPP with no specific studies in humans. In the New Zealand Household survey, Wilkins *et al.* (2006) found that 2.2% of the respondents could be described as dependent on (piperazines-based) "party pills" but cannot be related specifically to TFMPP. Animal studies found that TFMPP did not possess rewarding properties, reinforcing effects and did not substitute for cocaine, amphetamine (Fantegrossi *et al.*, 2005) but did substitute for S(+)-MDMA in self-administration and discrimination studies (Yarosh *et al.*, 2007). Therefore, it appears that TFMPP is unlikely to possess an abuse or dependence potential.

8. Abuse potential

There have been few studies regarding the abuse potential of TFMPP, with no specific studies in humans. Animal studies found that TFMPP did not possess rewarding properties, reinforcing effects and did not substitute for cocaine, amphetamine (Fantegrossi *et al.*, 2005) but did substitute for S(+)-MDMA in self-administration and discrimination studies (Yarosh *et al.*, 2007). Therefore, it appears that TFMPP is unlikely to possess an abuse or dependence potential.

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

In the 1970s, TFMPP was found to be a metabolite of antrafenine (2-[4-[3-(trifluoromethyl)phenyl]piperazin-1-yl]ethyl 2-[(7-(trifluoromethyl)quinolin-4-yl)amino]benzoate).

Antrafenine was an analgesic anti-inflammatory medicine comparable to naproxen (Berry *et al.*, 1983). During metabolism studies, it was suggested that due to its serotonergic effects, TFMPP may be partly responsible for its activity (Caccia *et al.*,

1985). Antrafenine may have been marketed in France under the proprietary name “Stakane” which seems to have been withdrawn with the development of newer compounds - but little information exists regarding this. TFMPP itself is not, and has not been, the subject of a marketing authorisation.

10. Listing on the WHO Model List of Essential Medicines

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

11. Marketing authorizations (as a medicine)

TFMPP has never been marketed as a medicine.

12. Industrial use

TFMPP 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 conducted in 2008 (Annex 1) shows that 3 countries, Denmark, France and Germany of the 49 countries responding, reported on the use of TFMPP in a harmful way. 16 countries reported that it is not used in a harmful way and in 17 countries this is unknown.

Germany reported that TFMPP is sold as a recreational drug as a “legal alternative” to illicit substances such as LSD and MDMA and also appeared as an additive in BZP products.

TFMPP use and seized material has been reported in various countries including USA, New Zealand and many in Europe (Denmark, Finland, Austria, UK, Sweden, Italy, France and Spain).

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

As for BZP, TFMPP 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) and 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) or other substances. Consequently, poly-substance use is common, with e.g. MDMA, cocaine or ketamine also detected in cases where toxicological analysis has been possible. In particular, the presence of additional substances is a common finding in both non-fatal and fatal cases. No hospital admissions were toxicologically proven to solely involve TFMPP.

15. Licit production, consumption and international trade

WHO questionnaire for review of psychoactive substances (2008) show that 3 countries legitimated TFMPP for technical use and none for medical or veterinary use.

16. Illicit manufacture and traffic and related information

Based on the report of the WHO questionnaire for review of psychoactive substances (Annex 1) 2008, 7 countries have tracked illicit activities involving the substance and clandestine manufacturing is reported one time.

17. Current international controls and their impact

Not applicable in relation to affecting impact of medical use.

18. Current and past national controls

European Union: not widely controlled at present (Feb 2008), except for; Belgium, Denmark, Greece and Sweden.

New Zealand: to be controlled

USA: controlled (Schedule I)

As of December 3rd 2005, TFMPP is illegal in Denmark.(multilingual archive) As of March 1 2006, TFMPP is scheduled as a "dangerous substance" in Sweden. TFMPP is unscheduled in the Netherlands. TFMPP was briefly emergency scheduled in Schedule I in the USA, but the scheduling expired in April 2004 and has not been renewed. Therefore, unlike its cousin benzylpiperazine, TFMPP is not currently an illicit substance in the USA. Based on the recommendation of the EACD, the New Zealand government has passed legislation which placed BZP, along with the other piperazine derivatives TFMPP, mCPP, pFPP, MeOPP and MBZP, into Class C of the New Zealand Misuse of Drugs Act 1975. A ban was intended to come into effect in New Zealand on December 18th 2007, but the law change did not go through until the following year, and the sale of BZP and the other listed piperazines became illegal in New Zealand as of 1st of April 2008. An amnesty for possession and usage of these substances will remain until October 2008, at which point they will become completely illegal

Recent data (Annex 1 - WHO questionnaire for review of psychoactive substances 2008) show that 6 countries reported TFMPP as controlled under legislation that is intended to regulate availability of substances of abuse.

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-trifluoromethylphenyl) piperazine (TFMPP)

The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for 1-(3-trifluoromethyl phenyl)piperazine (TFMPP) by 49 countries.

LEGITIMATE USE

Of the responded countries not one country authorized TFMPP as a medical or veterinary product.

3 countries legitimated TFMPP for technical use. In Australia it is used for forensic analysis. In the USA it is commonly used industrially as an intermediate in chemical synthesis and France also authorized TFMPP for technical use. No other legitimate use was reported. There is no information regarding the form, however in Germany TFMPP preparations in tablet and powder form were found along with other substances during the seizure of a laboratory.

Of the countries who reported Australia and Brunei indicated that they import TFMPP.

ABUSE

Of the 49 countries responding, 3 countries, Denmark, France and Germany reported on the use of TFMPP in a harmful way, 16 countries reported that it is not used in a harmful way and in 17 countries this is unknown.

Germany reported that TFMPP is sold as a recreational drug as a “legal alternative” to illicit substances such as LSD and MDMA and also appeared as an additive in BZP products. Doses between 25 and 100 mg are usual. Reports from experience describe doses up to 200 mg. No information on the extent of harmful use is available.

CONTROL

6 countries reported that TFMPP is controlled under legislation that is intended to regulate availability of substances of abuse. In Germany TFMPP is not subject of the drug control regulations. In cases of illegal production, circulation, trading or passing of TFMPP a violation of the Pharmaceuticals Act may be considered.

In total 7 countries have tracked illicit activities involving the substance. Clandestine manufacturing is reported one time. Smuggling is reported two times and diversion is not reported. Other illicit activities are reported only once. 6 countries reported on the quantity of the seizures. In the USA seizure data show that there are indications of abuse of this substance. From 2004-2008, there have been a total of 4,057 grams of powder seized. This substance is not designated as a controlled substance analogue under the Controlled Substances Act, therefore production of the substance intended for human use (i.e. abuse) can not be prosecuted in the USA.

IMPACT OF SCHEDULING

Scheduling is unlikely to have impact on medical practice since this substance is not used in any country as medicine for human or veterinary practice

Trifluoromethyl phenyl piperazine (TFMPP)

Brand Name

No information

Technical Use

- Forensic analysis
- Industrially as an intermediate in chemical synthesis