

# A Review on Benzylpiperazine and Trifluoromethylphenylpiperazine: Origins, Effects, Prevalence and Legal Status

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**ABSTRACT:** Since the uprising as a club and recreational drug in the United States in the 1970s, BZP and other piperazine related analogues has been gaining momentum as a new class of designer drug of abuse until they warranted their place as a controlled substance in several countries. However, such a status as a “legal” drug before has enabled them to penetrate the club scene across continents, and that the misperception of youth towards them as a safer alternative to MDMA or methamphetamine ensures their rampage. This review would take on benzylpiperazine (BZP) and trifluoromethylpiperazine (TFMPP) as the most popular member of the piperazines, focusing the discussion on their origins, pharmacokinetics and pharmacodynamics, their effects on the human body, their evasive legal status as well as their combination as a prominent drug cocktail. With such details comprehensively reviewed, hopefully it would cater for any needs of the effort to make these two compounds as a controlled substance in Malaysia.

**Keywords:** BZP, TFMPP, legal highs, designer drugs, Malaysia, piperazines

## Introduction

Designer drugs had been gaining ground in the recent years within narcotics industry, in which they had been employed as recreational drugs under names such as “Party Pills” or “Herbal Highs” (Thompson, Williams et al. 2006). Britannica Concise Encyclopedia defines a designer drug is a *synthetic version of a controlled narcotic substance that is has a molecular structure slightly different from that of some well-known controlled substance but whose effects are essentially the same, whereby the purpose of doing so is to avoid the drug being listed as illicit by law-enforcement organizations*. The Drug Enforcement Agency of the United States (DEA) applies a less glamorous name for such groups of drugs (Cooper), calling them as Controlled Substance Analogues (CSAs), which is dictated by the article 32 of the Federal Analog Act of the USA as a substance:

“(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;

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(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in Schedule I or II; or

(iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in Schedule I or II.”

However, this is not always the case as our drug of interest here, the piperazine analogues (**FIG. 1**) are actually not controlled substances nor related to any controlled substances in certain jurisdictions, for example, Ireland, Canada, Bulgaria and Malaysia (Nikolova and Danchev 2008; Freye 2009). Such a new class of designer drugs normally refers to benzylpiperazines, such as N-benzylpiperazine (BZP) itself, its methylenedioxy analogue 1-(3,4-methylenedioxybenzyl)piperazine (MDBP) and phenylpiperazines such as 1-(3-trifluoromethylphenyl)piperazine (TFMPP), 1-(3-chlorophenyl)piperazine (mCPP) and 1-(4-methoxyphenyl)piperazine (MeOPP) as the most commonly abused group of piperazine analogues.

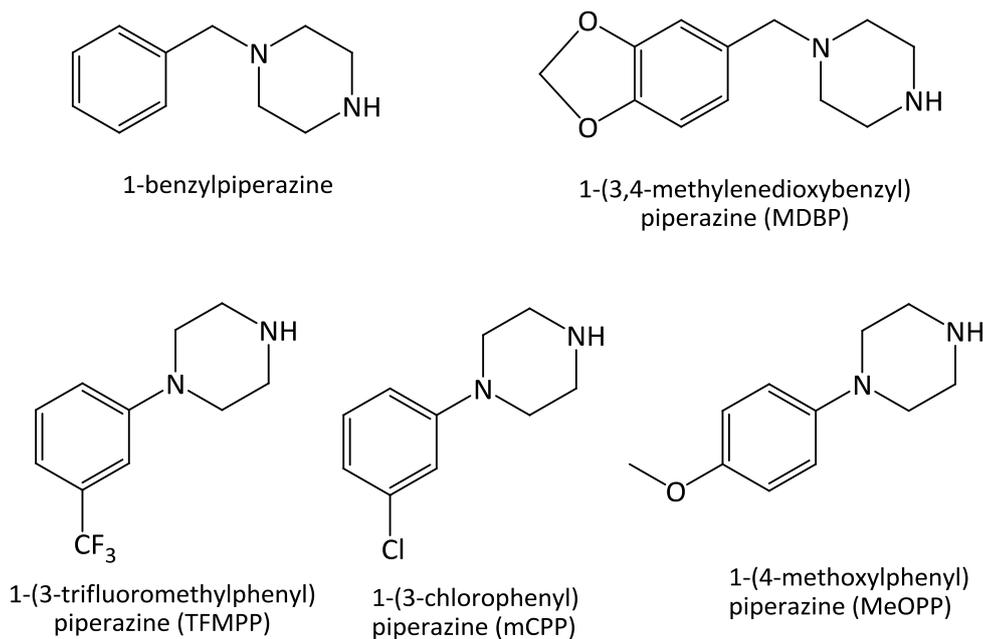


FIG. 1: General abused piperazine analogues

In order to formulate the party pills, these piperazines are usually mixed with caffeine and a range of vitamins and binders into tablets or capsules (Nikolova and Danchev 2008; EMCDDA 2009). Loose powders are also occurring while solutions are rarely encountered (EMCDDA 2009). They are sold in the black drug-market and in the names of “party pills”, “herbal highs” or “legal highs”, and sometimes as tablets of ecstasy or amphetamine (Kenyon, Button et al. 2007; Staack 2007). In general, piperazine blends are consumed, with the most prevalent being a mixture of BZP and TFMPP, although blends up to four different piperazines are available (Staack 2007). They sometimes are also mixed with other drugs of abuse including ecstasy, cocaine, amphetamine and ketamine (EMCDDA 2009).

Despite frequently marketed as “natural” and “herbal” highs, piperazines are actually purely synthetic chemical compounds consisting of a heterocyclic ring (1,4-hexahydropyridazine) (Nikolova and Danchev 2008). The piperazine ring and its derivatives are important cyclic components as raw materials in industrial fields for materials such as hardener of epoxy resins, insecticides, accelerators for rubber, urethane catalysts and antioxidants (Nikolova and Danchev 2008). Pharmaceutically, piperazines is one of the most potent drugs used as anthelmintics to treat round worms and is also the raw material in the synthesis of fluoroquinolone drugs such as norfloxacin and ciprofloxacin (Dessouky and Ismaiel 1974; Ramachandran and Kumar 1996).

However, the potential of piperazines as recreational drugs lies in their psychoactive properties, legal status and the perceived safety that ensued (Sheridan and Butler; de Boer, Bosman et al. 2001). The psychoactive properties of the piperazine containing compounds are caused by their ability to bind to the serotonin receptors of the human nervous systems (Glennon, Slusher et al. 1986). In the 1970s, derivatives of the piperazine containing compounds were further investigated but trials were stopped when it was discovered that benzyl derivatives had stimulant properties with the risk of abuse (Kenyon, Button et al. 2007). It is shown through research that the 1-aryl-piperazines show good binding affinity to serotonin receptors and such affinity has better selectivity with the appropriate ring substituents (Glennon, Slusher et al. 1986; Glennon 1987). This similar mode of action of the piperazines and the amphetamine type stimulants gives the desired effects of euphoria, alertness and social activeness that is much needed on the dance floor and thus achieve its status as party pills (Kenyon, Button et al. 2007; Staack 2007; Lucas, Fizmaurice et al. 2008), despite more and more countries had already restricted the usage of such substances, like the United States, Australia, New Zealand, Japan and parts of Europe (Freye 2009).

Despite the claim by certain literatures that BZP remains the main subject of interest in these party pills while mCPP, pMeOPP and TFMPP are only sold as free bases or as a salt in semi-bulk quantities and have not yet in pharmaceutical

formulations, recent seize reports from the Microgram (DEA 2009; DEA 2009) and other sources (Janes 2004; Kenyon, Button et al. 2007; Lucas, Fizmaurice et al. 2008; Nikolova and Danchev 2008) seem to picture the piperazine drugs as more of a cocktail, with TFMPP as the minor component, in a common ratio of 2:1, even though other ratios of combination are mentioned in uncertified sources.

A combination of BZP and TFMPP is always advertised as a MDMA substitute, due to the similar effects on the serotonin system, whereby a blend of both the drugs releases dopamine and serotonin from neurons via mechanisms dependant on dopamine transporters and serotonin transporters (Baumann, Clark et al. 2005). It is also reported that both the drugs acts in a synergy effect on each other, releasing far larger amount of dopamine than each drug induces alone (Baumann, Clark et al. 2005). And as such, the pill with its stimulating, hallucinogenic and euphoric properties, as well as its easy availability and so called “legal” status, has made its way into the club scene worldwide successfully (Inoue, Iwata et al. 2004).

### **Benzyloperazine: an introduction**

Even though the piperazine analogues as party pills have not achieved the notoriety enjoyed by the Amphetamine type stimulants, a plethora of academic works on it had already been produced, most probably due to legislation demands, as in the case of New Zealand, where the purchase of the drug has only been banned since April 2008, and in the process giving birth to a wealth of information by the nation’s researchers on the drugs, like those by Lucas, Fitzmaurice and Bassindale (Lucas, Fizmaurice et al. 2008) and Sheridan and Butler (Sheridan and Butler), just to mentioned a few.

Benzyloperazine was reported to be first encountered as a synthetic chemical in 1944 (Inoue, Iwata et al. 2004; Nikolova and Danchev 2008) used as a potential anthelmintic agent for farm animals with the creator identified by the European Monitoring Center for Drugs and Drug Addiction (EMCDDA 2009) as Burroughs Wellcome. Other source mentioned it as being synthesized from the pepper plant even though the species was not specified (Nikolova and Danchev 2008), however this is most likely not the case.

The interest on the medical liability of the compound was also investigated with clinical trials of it as early as 1950s (White and Standen 1953; Standen 1955). The drug as a round worm treatment agent was then forfeited as it is

discovered that it had side effects, presumably the amfetaminergic effects that was reported in the 1970s when it was investigated for its potential antidepressant ability in reversing the effects of tetrabenazine (a dopamine depleting agent) (Bye, Munro-Faure et al. 1973; Freye 2009). The liability of the drug for abuse had been discussed as well in other reports (Nikolova and Danchev 2008; Freye 2009). Ironically, a BZP analogue, N-ben-zyl-piperazine-picolinyl fumarate (Trelibet) was briefly marketed as an antidepressant in Europe despite such finding, BZP was identified as its metabolite (Magyar). BZP was also used a precursor to develop drugs against *Mycobacterium tuberculosis* (Bogatcheva, Hanrahan et al. 2006), as a main component for various other antimicrobial agents as well as for the synthesis of carbamoyl chlorides and unsymmetrical ureas for the synthesis of medical radiolabelled tracers (Lemoucheux, Rouden et al. 2003).

BZP is available either as the hydrochloride salt, a while solid crystals, or the base form, which is in the form of a slightly yellowish-green liquid (Freye 2009). The same author also mentioned that the liquid base is corrosive and causes burn, and thus, BZP was mostly commercially available in the dihydrochloride form (BZP-2HCl) (EMCDDA 2009). The researcher does not come across sources on the beginning of the compound as a drug of abuse, but Tsutsumi *et al.* (2005) stated that the earliest outburst of the drug was in the United States during the late 1990s, among youths using it as recreational or club drugs, due to its euphoric and stimulating effects (Tsutsumi, Katagi et al. 2005). The internet was also identified as the culprit (de Boer, Bosman et al. 2001; Inoue, Iwata et al. 2004) for the worldwide spread of the drug, in which it was marketed on the net in names like “A2”, “Herbal High” or “Legal High (de Boer, Bosman et al. 2001; Kenyon, Button et al. 2007). Other names associated with the drug were previously mentioned in this article. BZP was also often marketed as a dietary supplement to avoid stricter regulations despite that the fact it has zero dietary value (Freye 2009).

The EMCDDA (2009) noted the synthesis of BZP as:

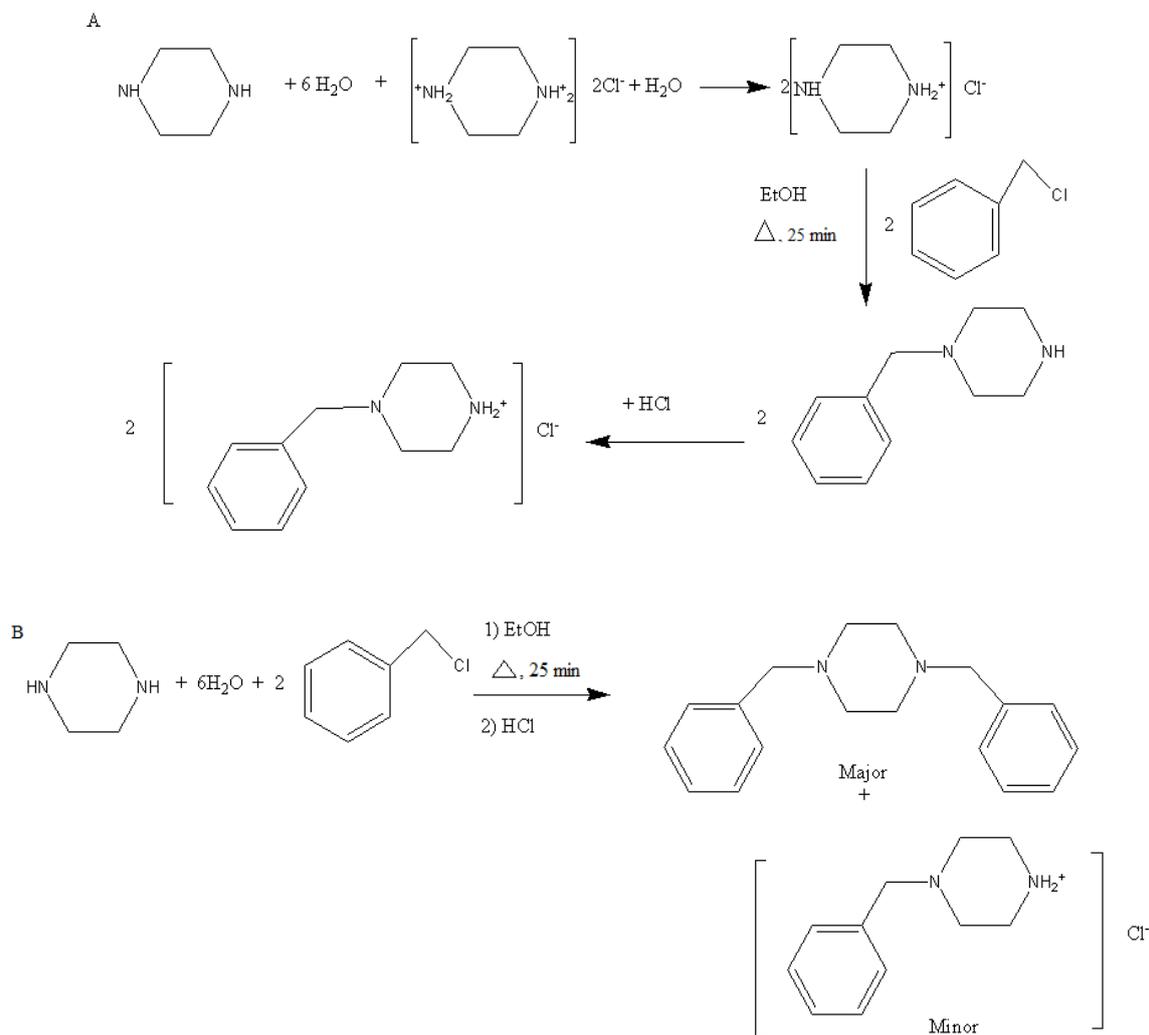
*“It can be manufactured by reacting piperazine monohydrochloride with benzyl chloride. The latter precursor is readily available, and piperazine monohydrochloride is easily produced from the commercially-available salts. It is known that 1,4-dibenzylpiperazine (DBZP) can be formed as a side-product in this reaction.”*

Bishop (2004) in an attempt to synthesize BZP dihydrochloride also described two commonly practiced clandestine methods for the synthesis of the drug:

*“The first synthesis method involved the mixing of equal molar amounts of piperazine hexahydrate, piperazine diHCl monohydrate and benzyl chloride. 1-BZP diHCl was the predominant product with a small amount of an additional compound,*

*1,4-dibenzylpiperazine. The second synthesis involved mixing equal molar amounts of piperazine hexahydrate and benzyl chloride. The predominant compound made from this method is 1,4-dibenzylpiperazine (Bishop 2004).”*

The synthesis route might be useful in the identification of impurities within the drug samples, **FIG. 2.**



**FIG. 2-** Clandestine synthesis routes for benzylpiperazine salts (Source and adapted from Bishop, 2004)

BZP has been available from retail chemical suppliers and that illicit synthesis has not been reported (Bishop 2004). In country where its purchase is legal, BZP products are produced in small specialist laboratories, whereby the raw materials could be commercially available from various chemical supply agencies and could be formed into tablets or capsules using relatively

cheap production techniques (Freye 2009). The same author also clarified through several literature pieces that despite the substance was advertised as a natural product, in terms like “pepper extract” or “herbal product” by the retailers, it is known to be entirely synthetic (Gee and Fountain 2007) and not to be found occurring naturally (Alansari and Hamilton 2006). BZP is on sale as a labelled

ingredient in a wide number of products on sale across the internet, under names such as “BZP”, “A2”, “Legal E”, “Legal X”, “Frenzy” and “Nemesis”. (Inoue, Iwata et al. 2004; Freye 2009)

#### *Pharmacodynamics and pharmacokinetics*

Baumann et al. (2006) describes the compound as having a mixed mode of action, acting on the serotonergic and dopaminergic receptor systems in a similar fashion to MDMA (Baumann, Clark et al. 2006). BZP induces a central serotoninomimetic action on the body, which involves serotonin (5-HT) uptake inhibition and 5-HT<sub>1</sub> receptor agonistic effects (Tekes, Tothfalusi et al.). BZP binds to 5HT<sub>2A</sub> receptors and causes its mild hallucinogenic effects at high doses, while binding to the 5HT<sub>2B</sub> receptors explains the peripheral side effects experienced, like stomach pains and nausea as the receptor is densely available in the gut (Nikolova and Danchev 2008). Its binding to 5HT<sub>3</sub> receptors causes the common side effects of headaches, as the receptor is acknowledged to be in the development of migraine headaches (EMCDDA 2009).

BZP has amphetamine-like actions on the serotonin reuptake transporter, which increases serotonin in the extracellular fluids surrounding the cell and thus, induces the activation of the surrounding receptors, leading to the stimulating and euphoric effects of amphetamines (Tekes, Tothfalusi et al.; Lyon, Titeler et al. 1986). Within the studies by Bauman et al. (2005), dopamine was discussed as another neurotransmitter that was released by the pharmacology actions of BZP, even though its potency is lower than that of methamphetamine (Baumann, Clark et al. 2005). Since its mechanism is claimed to mimic that of MDMA, it could have served as a substrate for the dopamine transporter, triggering nonexocytotic release of transmitter molecules from dopamine neurons (Pomara, Willoughby et al. 2005).

Besides prominent serotonergic and dopaminergic effects of BZP, other implications include the resting and nerve-evoked release of noradrenaline by acting as an antagonist at the alpha-2-adrenoreceptor, like yohimbine, which inhibits negative feedback, causing an increase in released noradrenaline (Magyar). Noradrenaline is the major neurotransmitter behind the “fight or flight”, having cardiovascular effects like increase heart rate as well as blood pressure. It is interesting to note that despite having the similar chemical structure, unlike Viagra, BZP does not have any effect on sexual performance (Nikolova and Danchev 2008).

The enzymes CYP2D6 and COMT was identified to metabolize BZP according to Gee and Fountain (2007) (Gee and Fountain 2007), supported by Staack et al. (2002) who did a research on the metabolism and toxicological detection of the N-benzylpiperazine metabolites in human and rat urine, and found out that 4-hydroxy-BZP, 3'-hydroxy-BZP, piperazine, 4'-hydroxy-3'-methoxy-BZP and benzylamine as among the metabolites (Staack, Fritschi et al. 2002). The same author also mentioned that some of the metabolites are excreted as glucuronic and/or sulphuric acid conjugates. For the pharmacokinetics aspect of the drug, Antia et al. (2009) to date, has been the sole contributor to the knowledge with regards to human body interaction to the drug (Antia, Lee et al. 2009). The literature stated a low bioavailability of the drug, in which the urine only accounted for 12.5% of the dose administered and the drug could be detected in the human plasma for up to 30 hours of an oral dose intake.

Apart from MDMA, BZP was also identified as an analogue to other amphetamine type stimulants as well. A double blind study in 1973 found that amphetamine addicts could not differentiate between equipotent doses of amphetamine and BZP (Campbell, Cline et al. 1973). In a recent research using hooded rats, BZP's acute effects was also shown to be that of many similarities to methamphetamine, only that the latter might shown more potency, thus indicating the possible risk for abuse and drug dependence for BZP as in the case of methamphetamine (Herbert and Hughes 2009).

#### *Effects of BZP use*

BZP is typically taken with the other piperazines, even though it could be abused alone for its stimulant effect (Bye, Munro-Faure et al. 1973; Campbell, Cline et al. 1973). Due to its similar mode of action to MDMA, both animal and human studies have demonstrated that the pharmacological effects of BZP are qualitatively similar to that of amphetamine; while taking alone, BZP acts as a mild stimulant, with a potency of 10% of the strength of normal “speed” or amphetamine, giving effects like tachycardia and systolic blood pressure (Bye, Munro-Faure et al. 1973; Campbell, Cline et al. 1973; Nikolova and Danchev 2008). BZP is often taken in the form of ingestion of powder, tablets or capsules, while other route of administration was reported as smoking or snorting (Nikolova and Danchev 2008). Users of BZP reported wakefulness, euphoria, increased vigilance, alertness and a general feeling of well-being as the effects of BZP. Perception of the sensations such as taste, colour or music may also be subjectively enhanced (Nikolova and Danchev 2008).

As with most sympathomimetic stimulants, there appears to be a full spectrum of adverse side effects associated with BZP use. Nikolova and Danchev (2008) listed down the side effects as: insomnia, mild to severe hangover after the drug effects wears off, dilated pupils, dryness of the mouth, extreme alertness, pruritus, confusion, agitation, tremor, dystonia, headache, dizziness, anxiety, insomnia, vomiting, chest pain, tachycardia, hypertension, palpitations, collapse, hyperventilation, hyperthermia, and problems with urine retention (Nikolova and Danchev 2008). The more severe toxic effects associated with the drug included psychosis, renal toxicity and seizures, prolonged QTc intervals, hyponatraemia, agitation, palpitations and panic attacks (Gee, Richardson et al. 2005; Nikolova and Danchev 2008). Austin and Monasterio (2004) reported a case of acute psychosis when BZP is taken together with cannabis and nitrous oxide (Austin and Monasterio 2004). Fatalities by the administration of BZP alone or BZP with other piperazine blends are not reported. However, cases in which fatalities do occur when the drug is taken with other drugs, and/or alcohol (Balmelli, Kupferschmidt et al. 2001; Elliott and Smith 2008).

BZP is reported as “not very addictive”, in which animal studies have indicated that it has weaker addictive effects if compared to methamphetamine (Brennan, Lake et al. 2007). Nikolova and Danchev (2008) mentioned that “due to tiredness associated with the body’s recovery from stimulants, such as BZP, it is common for users to be able to sustain a week-long intake” (Nikolova and Danchev 2008). A survey in New Zealand classified one in every 25 (2.2%) as dependant on it, while 97.9 % of the users said that “it would be difficult to stop using legal party pills”, one of the reason being that BZP is perceived more safety than methamphetamine (Brennan, Lake et al. 2007). In spite of this, we could not regard the drug as non-addictive as the endogenous release of dopamine/ serotonin caused by the drug as in MDMA, MDA and cocaine are known to exert addictiveness and such a liability is observed in rhesus monkeys (Fantegrossi, Winger et al. 2005). Research on tolerance effects of the drug was scarce, with only the survey from Thompson et al. (2006) showing one fifth of the abusers exhibiting tolerance or withdrawal symptoms (Thompson, Williams et al. 2006).

### **TFMPP: an introduction**

TFMPP(1-(3-trifluoromethylphenyl)-piperazine) is claimed to be the most abused compound of the piperazine-derived compound besides BZP (Staack, Fritschi et al. 2003). The substance was first encountered as a chemical intermediate in the

synthesis of pharmaceutical products (Tsutsumi, Katagi et al. 2005). In the literatures and the internet, it had the reputation of mimicking psychoactive or hallucinogenic properties of MDMA (Herndon, Pierson et al. 1992; DEA 2002; Staack, Fritschi et al. 2003). Staack, Fritschi and Maurer (2003) (Staack, Fritschi et al. 2003) also cited a few sources regarding animal studies that partly support the claim (Schechter 1988; Boja and Schechter 1991; Herndon, Pierson et al. 1992).

### *Pharmacodynamics and pharmacokinetics*

Preclinical findings established that TFMPP is a non-selective postsynaptic 5-HT receptor agonist, with the drug exhibiting modest binding affinity (B100nM) for 5-HT1 and 5-HT2 receptor subtypes (Fuller 1988; Hoyer 1988). Apart from that, TFMPP was also reported to display presynaptic actions like the stimulation of SERT-mediated serotonin release from neurons, demonstrated by *in vitro* studies (Pettibone and Williams 1984) and *in vivo* studies (Auerbach, Rutter et al. 1991). As for a more general mechanism of action, the pharmacological behaviour of TFMPP is summarized by Nikolova and Danchev (2008) as similar to phenethylamines (MDMA, MDE); behaving in a manner of non-selective serotonin agonist, in the same time blocking serotonin reuptake as well as enhancing its release., all contributing to increase levels of serotonin (Nikolova and Danchev 2008). The resulting anxiogenic and panic attack reported could be supported by animals and human studies on structurally related compounds (Kennett, Whitton et al. 1989; Murphy, Lesch et al. 1991; Zuardi 1991; Wallis and Lal 1998).

The metabolism of TFMPP was studied by Staack, Fritschi and Maurer (2003), in which TFMPP was proven to be extensively metabolized, mainly by hydroxylation of the aromatic ring and by degradation of the piperazine moiety to *N*-(3-trifluoromethylphenyl) ethylenediamine, *N*-(hydroxy-trifluoromethylphenyl) ethylenediamine, 3-trifluoromethylaniline, and hydroxy-3-trifluoromethylaniline, while phase II reactions included glucuronidation, sulfatation and acetylation of phase I metabolites (Staack, Fritschi et al. 2003).

### *Effects of TFMPP use*

TFMPP is not useful medicinally, but is purportedly sold as a recreational drug as a “legal alternative” to illicit drugs such as LSD and MDMA (Nikolova and Danchev 2008). This might be due to the reason that it has properties similar to the stimulant effects of ecstasy, but in larger doses it could even promote hallucinogenic effect

(Nikolova and Danchev 2008). A single dose of TFMPP taken was as having the moderate psychoactive effects as being “somewhere between empathogens such as MDMA and entheogens such as psilocybin, mescaline, or LSD”(Nikolova and Danchev 2008) and therefore poses an even greater risk to young adults because to achieve the hallucinogenic effects as in taking MDMA, they faced the danger of accidentally overdosing themselves.

Despite of that, TFMPP is still a drug with mild effects and is rarely administered by itself, and thus little research has been done on it as a single drug. According to Nikolova and Danchev (2008), TFMPP produces adverse effects in animals rather than self-administration and thus, the Drug Enforcement Agency of the United States (DEA) during the review in 2004 did not group TFMPP as an illicit drug in Schedule I. The research by Baumann et al. (2005) supports such a claim that TFMPP is at least three-fold less potent than that of MDMA in its ability to stimulate release of endogenous 5-HT; and it is less efficacious than MDMA, by which the drug fails to produce large elevations in dialysate 5-HT, even at large doses (Baumann, Clark et al. 2005).

It is the effect brought up by the combination of BZP/TFMPP in most party pills that concerns us the most. Such a cocktail of drugs is said to produce feelings and euphoria and energy as well as a desire to socialize, thus gaining its popularity as rave drugs (Maurer, Kraemer et al. 2004). The combination ratio was well known to be 2:1, even though other ratio of combinations like 3:1 were cited, which were all advertised as a MDMA substitute (Russell 2006; Thompson, Williams et al. 2006; Nikolova and Danchev 2008).

### **BZP/TFMPP as a cocktail**

The findings of Baumann et al. (2005) suggested that the combination of BZP and TFMPP releases dopamine and serotonin from neurons via mechanism dependent on dopamine transporters and serotonin transporters, creating the experience as that of MDMA in take due to the similar mechanisms (Baumann, Clark et al. 2005). However, the most significant discovery of the research was the synergism between BZP and TFMPP, whereby when both the drugs taken together recorded an endogenous release of dopamine overwhelming the amount released when the drug was taken alone. The research also highlights the inhibitory capability of the postsynaptic actions of TFMPP, while may produce *in-vivo* behavioural effects different from those of MDMA.

A combination of BZP/TFMPP was illustrated as having entactogenic body-effects similar to MDMA and/or MDEA, but generally without the strong empathogenic qualities of these phenethylamines (Nikolova and Danchev 2008). Among the experiences described by the authors were a meditative quietness, calm centeredness, contentedness, a warm flushing sensation, waves of euphoria, tactile pleasure, time dilation, and mild visual effects (similar to low-dose mescaline, LSD). Baumann et al. (2005) also noted that a 3mg/kg dose of BZP/TFMPP is sufficient to mirror the effects of MDMA (Baumann, Clark et al. 2005).

Apart from its delicate replica of experience to MDMA, the BZP/TFMPP could not escape from side effects as per in the case of serotonergic drugs. A range of side effects that has been associated with the drugs, including nystagmus, dehydration, seizures, jaw-clench, mild to severe nausea, vomiting, toxic psychosis (panic and extreme paranoia), high blood pressure, persistent headache, flu-like symptoms, stiff neck, post-trip exhaustion, impotence, anxiety, migraine muscle aches, as well as a come-down syndrome characterised by insomnia and loss of appetite (Nikolova and Danchev 2008).

Literature on human clinical trials on the mixture was not encountered by the researcher, however, the animal study conducted by Baumann et al. (2005) highlighted the concern of safety regarding the combination, as seizures in rats at a dose of 10mg/kg; which is just three-fold greater than the threshold dose for monoamine-releasing activity, indicating a narrow window of safety (Baumann, Clark et al. 2005). This could indicate potential dangerous consequences for human users of the drug, even though for now no fatality has been reported for consuming BZP/TFMPP alone.

Side effects of a drug tend to be significantly worsened when alcohol is consumed with the drugs, especially headache, nausea and hang overs (Nikolova and Danchev 2008). These side effects might discourage the abuse of TFMPP, even though it is difficult to say how many of these side effects are actually produced by TFMPP itself, as anxiety, headache and nausea are common to all piperazine drug (Nikolova and Danchev 2008). However, the authors also noted that users had complained that pills containing TFMPP may lead to a more severe hangover if compared to those with BZP alone.

### **Legal status of BZP and TFMPP**

Piperazine related analogues has reach a level of worldwide distribution in 1990s and early decade

of the 21st due to its easy availability through the internet and so called “legal status”, as supported by various seizures reported by authorities like the DEA (2007) (DEA 2007) and the EMCDDA (2009)(EMCDDA 2009), just to name a few. The infestation of the drugs, in which BZP being the most notorious of them all, led to its temporary placement along with TFMPP into the Schedule I of the Controlled Substance Act (CSA) of the United States in year 2002, followed by the final placement of BZP in Schedule I in 2004. (DEA 2007) Japan responded imminently to the threat as well, and since October 2003, BZP and mTFMPP are placed under control. Australia and New Zealand (as of April 2008) also have the drug banned throughout country (Freye 2009).

The European countries have been relatively late in terms of the regulation of the drugs, whereby by the time the joint report of the drug by the Europol and EMCDDA was released in 2007, only eight members of the European Union (Belgium, Denmark, Estonia, Greece, Italy, Lithuania, Malta and Sweden) had the substance regulated under drug control (EMCDDA 2008). A subsequent decision by the EU drugs agency following the report calls for its member states to “take, within one year, the necessary measures to submit BZP to: control measures proportionate to the risks of the substance” and ‘criminal penalties’ in line with their national laws (which in turn comply with the UN drug conventions) (EMCDDA 2008). France complied with the decision on May 2008 while the United Kingdom has decided to ban BZP and *gamma*-Butyrolactone (GBL) by the end of 2009 (AFSSAPS 2008; BBC 2009). In contrast, countries like Canada and Ireland as well as Malaysia, still does not in any way regulate the use of the drug (Freye 2009; Murphy, Antia et al. 2009).

### **Prevalence of the drugs**

The significance in putting the drugs in the control of the law lies in two factors. First, its prevalence throughout the world; and second, a legal status would give in to the misconception that the drug is safe. The following is a few citations on the degree of infestation of the drugs. Since 2001, DEA forensic laboratories analyzed 128 drug exhibits from 59 law enforcement cases pertaining to the trafficking, distribution and abuse of BZP. The analysed drug exhibits comprised of 66,645 tablets, 8,409 capsules and 356,997.1 grams of powder (DEA 2007). The EMCDDA (2009) stated that 15 of its member states have reported the seizures of BZP, ranging from small amounts to a case whereby a single seizure of 64900 tablets that occurred in London (EMCDDA 2009).

According to the British Forensic Service, in the first half of 2009, the number of seized tablets containing piperazines was higher than the ones containing MDMA, indicating the possibility that a legal status might add to the growth of the drug distribution (EMCDDA 2009). A review by the Europol and EMCDDA (2007) on BZP has also noted that the supposedly United Kingdom-based online shops are the main source of BZP-containing products for the recreational users (Europol and EMCDDA 2007). To better understand the situation, a New Zealand Household Survey of Legal Party Pill Use conducted in 2006 indicated that one out of five persons within a sample of 2010 individuals has ever tried the legal party pills, with the prevalence at the most in the age group of 18-24 (Wilkins C 2006). This is further supported by a conservative estimate in 2005 that 150,000 doses of party pills/legal herbal highs are sold in New Zealand every month (Bowden 2005).

### **The perception of safety for “Legal Highs”**

Sheridan and Butler (2009) provided a very useful insight into the perception of young adults on legal drugs (Sheridan and Butler, 2009). The implications of a drug being conferred the legal status for one would lead some conflicting messages to the young adults. A few harmful perceptions would be that the drug would be safe or quality assured, or that it would have an inferior effect due to the sanctioning of the government, thus could be taken in larger quantities, which would lead to devastating effects, as mentioned in the review on the health effects of BZP in above. Being legal for certain individuals also mean that taking the drugs is ‘socially acceptable’, as they are widely available. Such a phenomenon of wide availability, in which the products are sold by designated retailers or in specialized shops, with the contents visibly stated, also fostered the perceived safety of the drugs (Europol and EMCDDA 2007). All of these implications should be taken into account as the factors of urgency needed in giving the drugs a controlled status in Malaysia, as a “legal high” reputation might lead to a potential harm reduction perception in the youths.

### **What is in a typical BZP/ TFMPP pill?**

It is important to understand the approximate contents of a BZP tablet. A reported dose of 100 mg of BZP is said to have effects of between 6-8 hours duration, while in doses between 75 and 150 mg BZP effects like arousal, euphoria, wakefulness, improved vigilance and feeling of wellbeing could be produced (Europol and EMCDDA 2007).

However, this does not stop the fact that the dose of BZP products has been steadily increased since their introduction in New Zealand, from a standard dose of 70-80 mg to 250 per session (Perrott 2005; Wilkins C 2006). Table one is the review by Thompson et al., (2006) on the recommended dose of BZP that could be taken by the party pill industry (Thompson, Williams et al. 2006).

In terms of the European market, the Europol and EMCDDA (2007) joint report on BZP quoted the study on the normal dosage of BZP found within the party pills purchased from internet suppliers:

“A team from St. George’s University of London purchased and analysed different tablets and capsules from three major internet suppliers. The study found that of the 26 tablets and capsules screened, 23 contained one or more of the following piperazines: BZP, TFMPP, pFPP, pMPP, mCPP and DBZP. BZP was present in 21

of the 23 piperazine-containing tablets/capsules. Additional ingredients were nicotineamide in capsules and caffeine in tablets. The most common combination both in the capsules and in the tablets was BZP with TFMPP. The quantification of BZP and TFMPP in tablets and capsules (n=20) gave a mean BZP of 65mg and TFMPP of 22mg. However, the range varied widely between 28–133mg BZP and 4–72mg TFMPP. The content stated on the packaging for BZP ranged from 105mg to 200mg, and for TFMPP from 50mg to 75 mg (Europol and EMCDDA 2007).”

A separate investigation by de Boer et al. (2001) also quantitated a A2 capsule which contains 86.4 mg of BZP, in agreement with declared amount of 125mg of BZP dihydrochloride, corresponding to 88mg of the free base (de Boer, Bosman et al. 2001).

**TABLE 1:** Industrial recommended dose of popular party pills in New Zealand (Source and adapted from Thompson et al., 2006)

Trade Name	BZP/Tab	TFMPP/Tab	Recommended Consumption (tablets)	Maximum Recommended dose
Charge	75mg	5mg	2 then a further 2 in 2-3 hours if tolerated	300mg BZP 20mg TFMPP
Jet	85mg	10mg	2	170mg BZP 20mg TFMPP
Bliss	50mg	25mg	3	100mg BZP 50mg TFMPP
Jet + Bliss Mix	2 Bliss and 1 Jet Capsules Dose above		3	185mg BZP 60mg TFMPP
Kandi	90mg	Not Specified	2, wait 2h, then another 2 if tolerated	360mg BZP
Rapture	75mg	25mg	2, wait 2h, then another 2 if tolerated	300BZP 100mg TFMPP
Frenzy	75mg	-	2, wait 2h, then another 2 if tolerated	300mg BZP
The Grunter	200mg	20mg	1	200mg BZP 20mg TFMPP

The New Zealand researcher contribution to the understanding does not stop short of survey on the prevalence of the drugs and its adverse effects, Russell (2006) made a review on the various ingredients that is contained within a tablet of the party pills (Russell 2006). Electrolytes, amino acids and herbal extracts such as Black Pepper or Ginseng Extract were said to be added to promote the image of the drug being natural and healthy, and therefore perceived safe. He cited the example of the drug “Frenzy” with its content as follows:

- Benzylpiperazine: 50mg
- Amino Acids: 410mg (Glutamine, Phenylalanine, Tau-rine, Tyrosine, Glycine, Alanine, Tryptophan, Aspartic Acid)
- Piper Nigrum Extract: 40mg
- Capsicum Annum Extract: 32mg

- Paullinia Cupana Extract: 40mg

Paullinia Cupana sp. is also known as Guarana, contains guaranine and is more commonly known as caffeine, a substance that is widely available as an extract from coffee bean or tea leaf, a common adulterant used in drugs.

Another trade brand of the piperazine “Altitude” which comes as a pack of six tablets along with a recovery pack contained:

- Piperazine blend: 60mg (Often a combination of BZP/TFMPP in a 3:1 ratio)
- Amino Acid Blend: 100mg
- B vitamins: 34 mg
- Vitamin C, Minerals, Citrus biflavonoid, Ginseng extract

Seizure reports from all over the Europe reported various combinations of piperazines together with BZP, most notably TFMPP (Denmark, France, Greece, Ireland, the Netherlands, and the United Kingdom), but also MeOPP (Denmark and the Netherlands), mCPP (the Netherlands) and DBZP (the Netherlands and the United Kingdom). (Europol and EMCDDA 2007) Besides that, various other substances were also reported to be encountered in combination with BZP-tripelenamine (Azarone; an antihistamine), cocaine, caffeine, 2-phenylethylamine (2-PEA), MDMA etc.

The data from the Swedish Police, Customs and the National Board of Forensic Medicine – Department of Forensic Chemistry noted that various forms of BZP were retrieved in seizures, ranging from white powders to different shades of colour, sometimes as pure BZP and sometimes mixed with other substances. Capsules of different types consisting of mixtures of various kind of substances as well as tablets of different types and colours were encountered. Ketamine, N-methyl-N-benzylpiperazine, sildenafil, phenazone, chavicine (a constituent of black pepper), dextromethorphan, TFMPP, cocaine, steroids, ephedrine and caffeine were among the adulterants encountered by the Swedish authorities during seizures of powders, tablets or capsules. Caffeine was singled out as the most common detected excipients, in which 99% of all seizures reported such a finding. In subsequent to all these information obtained, it is vital for any analysing method designed for the compounds to have the ability to extract, resolve and quantitate BZP and TFMPP from the other substances occurring in the mixtures.

## Conclusion

It is of little doubt that due to the interconnected nature of the world that piperazine tablets might soon appear to be another matter of concern for the narcotic officers in Malaysia. Thus, it would be advisory that Malaysia takes the same measure as its European counterparts to ban the substance through legislation, curbing any chances of the drugs taking the legal loophole for its own marketing. A search of the internet shows that there are chemical suppliers of BZP and TFMPP ready to sell the compounds in their salt form, making it extremely easy for the drug dealers to produce tablets of their own by simple tableting procedures. As certain piperazines are viable for medicinal purposes, strict enforcement at the immigration level would need to be done to prevent the entry of these compounds, if it must, involving chemical identification analysis as well. No doubt, this could all be only done under a legal framework, so the lawmakers should be aware of such a potential

threat. Forensic scientists and narcotic officers might want to add the piperazines into their agenda as well, as one of the drugs to be screened for whenever a room of doubt arises. When dealing with designer drugs that does not get tired from revamping themselves, it is always about the awareness on the global drug market and hopefully, this review permits for some basic understanding of BZP and TFMPP as pioneers of a new class of designer drugs.

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