N-Benzylpiperazine (BZP)

Critical Review Report

Agenda item 4.2

Expert Committee on Drug Dependence

Thirty-sixth Meeting

Geneva, 16-20 June 2014

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Contents

Summary

N-Benzylpiperazine (BZP) is a piperazine derivative with stimulant properties (including euphoria). BZP has never been licensed as a medicine but was found to be an active metabolite of a proposed anti-depressant (piberaline), later discontinued. Abuse was first reported in the late 1990s in the USA and Scandanavia but has since been reported in many other countries (particularly New Zealand, Australia and in Europe). The mode of abuse is similar to that of "Ecstasy" with many users seeking MDMA-like effects. Many suppliers of BZP market(ed) the drug as "legal Ecstasy" or as a "legal high". Such products typically contain other piperazine derivatives in variable quantities. Toxic effects (agitation, tachycardia and seizures) have been reported in users with associated hospital admissions, but cases involving BZP alone are rare. Although BZP has been detected in fatalities, owing to the manner of death and/or the presence of other drugs, it has been difficult to specifically determine the toxicological significance of BZP in these instances. Animal studies have indicated both an abuse and dependence potential for BZP but human clinical studies are currently too limited to support this.

1. Substance identification

A. ***International Nonproprietary Name (INN)***

Not applicable

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

Free base: 2759-28-6

Monohydrochloride salt: 72878-35-4

Dihydrochloride salt: 5321-63-1

C. ***Other Names***

benzylpiperazine

1-benzylpiperazine

N-benzylpiperazine

1-benzyl-1,4-diazacyclohexane

D. ***Trade Names (hydrobromide salt)***

None

E. ***Street Names***

BZP has been associated with various street names including “A2", "Legal E", "Legal X", “Herbal High” and numerous brand names relating to its availability as a perceived legal “Ecstasy” alternative (e.g. “PEP”, “Nemesis”, “Twisted”, “Flying Angel” and “Wicked High”), although this changed following control in various countries.

F. ***Physical properties***

BZP base is a pale, slightly yellowish-green, corrosive liquid, which can cause burns; the hydrochloride salt is a white solid and an irritant to the eyes (DEA, 2006).

G. ***WHO Review History***

BZP was pre-reviewed at the 35th ECDD meeting and based on the reported psychostimulant effects, evidence of abuse and adverse effects, the Expert Committee concluded that a critical review was warranted.

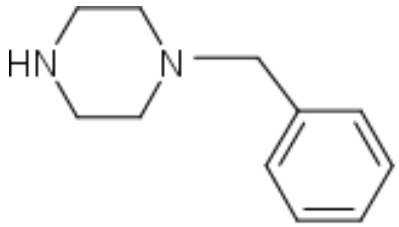
2. Chemistry

A. ***Chemical Name***

IUPAC Name: 1-benzylpiperazine
CA Index Name: 1-benzylpiperazine

B. Chemical Structure

Free base:



Molecular Formula: $C_{11}H_{16}N_2$
Molecular Weight: Free base = 176.26; Dihydrochloride salt = 249.19
Melting point: 181-182° C (base); 281-282°C (dihydrochloride)
Boiling point: not known
Fusion point: not known

C. Stereoisomers

BZP has no chiral centres and therefore no stereoisomers.

D. Synthesis

BZP is an entirely synthetic compound and has been available from retail chemical suppliers (e.g. Sigma-Aldrich). Chemical synthesis is relatively straightforward by reacting piperazine monohydrochloride with benzyl chloride (Craig and Young, 1973). Piperazine citrate (a commercial antihelminthic) as well as its commercially-available dihydrochloride and phosphate salts can be converted to piperazine monohydrochloride salt. 1,4-Dibenzylpiperazine (DBZP) may be produced as a side-product during the manufacturing process and has been found in some BZP-containing tablets.

E. Chemical description

BZP is an aryl-substituted piperazine. It is normally produced as the dihydrochloride salt. Like other aryl-substituted piperazines, it is not directly related to any of the more common substances of misuse, but has a more distant connection with phencyclidine and with 1-phenylethylamine and its derivatives (King et *al.*, 1996).

F. Chemical properties

See Section B and G.

G. Chemical identification

Extraction and analysis of BZP and other piperazines is relatively straightforward given their chemically basic nature and structure making them amenable to a number of techniques. Detection methods such as capillary electrophoresis (CE), gas chromatography with mass-spectrometry (GC-MS), high performance liquid chromatography with diode-array detection (HPLC-DAD) and/or mass-spectrometry (LC-MS), infra-red spectroscopy (IR) and thin layer

chromatography (TLC) have been published (de Boer *et al.* 2001, Elliott and Smith 2008, Antia *et al.* 2010, Bishop *et al.* 2005). The detection outputs depend on the technique used but for BZP, the underivatised GC-electron impact mass spectrum has ion peaks at (m/z) = 91 (base peak); 134, 56, 176 and 65. Similarly, with LC-MS, the pronated molecular ion [M+H] of 177 m/z is observed with fragmentation resulting in the predominant 91 m/z ion. For presumptive tests, BZP does not give a colouration with Marquis or Scott's field tests, but does give a positive reaction with Nitroprusside reagent. There is also some cross-reactivity with commercially-available urine immunoassay tests for metamfetamine (Kenyon *et al.* 2007). As indicated above, although various techniques have been reported, primarily GC-MS and LC-MS have been used for the identification and quantification of piperazines in body fluids (de Boer *et al.* 2001, Staack *et al.* 2002, Tsutsumi *et al.* 2005, Antia *et al.* 2010, Peters *et al.* 2003, Inoue *et al.* 2004, Nordgren *et al.* 2005).

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

4.1. Pharmacodynamics

Overall, animal and human studies have concluded that BZP is a monoaminergic stimulant drug with effects comparable to amphetamine.

Neuropharmacology and effects on central nervous system

Animal studies have demonstrated that BZP stimulates the release and inhibits the reuptake of dopamine (DA), serotonin (5-HT) and noradrenaline (NA), but dopaminergic and serotonergic effects predominate. During these studies, BZP was found to be less potent than MDMA, metamfetamine or amfetamine.

Specifically, with regard to the adrenergic system, rabbit studies found BZP to be an α2-adrenoreceptor antagonist thereby inhibiting the presynaptic negative feedback mechanism (yohimbine-like and tyramine-life effect) (Magyar 1987 and Magyar et al., 1986). However, an in vitro study using cortical slices of rat brain showed no presynaptic 2-adrenoreceptor antagonistic effect of BZP (Szucks *et al.,* 1987). Nonetheless, both studies and further work found BZP potentiated the nerve-evoked release of NA (Magyar 1987; Magyar *et al.,* 1986 and Szucks *et al.,* 1987). Tekes *et al.,* (1987) also showed that BZP released NA as well as inhibited the high-affinity uptake of NA. All of these studies were part of an assessment of the action of EGYT-475 (piberaline).

With regard to the dopaminergic and serotonergic systems, although BZP was found to inhibit the high-affinity uptake of DA and NA, it had a particularly significant blocking effect on 5-HT reuptake in rats (Magyar 1987; Tekes *et al.,* 1987). The latter group concluded that BZP had no effect on 5-HT_2 receptors and both inhibition of 5-HT uptake and 5-HT_1 receptor stimulation contributed to its central serotoninomimetic effect. During further studies of BZP as a metabolite of piberaline, BZP was found to have 5-HT antagonistic and partial agonistic properties (Malomvolgyi *et al.,* 1991). A

study of dopamine-induced circling behaviour in acutely lesioned rats indicated BZP produced contralateral turns by the release of newly-synthesised DA (Oberlander *et al.,* 1979).

Later studies in rats found BZP caused the release of a dopamine transporter substrate (^{3}(H)MPP$^+$) in vitro and produced an in vivo increase in extracellular DA and 5-HT: the latter only at a high dosage (Baumann *et al.,* 2004; Baumann *et al.,* 2005). This was noted to be reminiscent of metamfetamine. TFMPP was found to be a selective releaser of 5-HT transporter substrate (^{3}(H)5-HT) and increased extracellular 5-HT. Administration of BZP and TFMPP at a 3 mg/kg dose (1:1 ratio) produced parallel increases in 5-HT and DA, mirroring the results observed with MDMA. A higher dose of 10 mg/kg BZP:TFMPP (1:1) increased DA to a higher degree than the drugs alone, with some rats developing seizures. 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).
Hyperthermia and muscle contraction was also observed during rat studies (Tekes *et al.,* 1987 and Magyar *et al.,* 1986).

Hashimoto et al., (1992) found that administration of BZP to rats reduced the levels of 5-HT and 5-hydroxyindole acetic acid in the cerebral cortex of animals that had previously been injected with MDMA, leading to the possibility that BZP might provide some protection against the neurotoxic effects of MDMA.

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, BZP has been shown to be a powerful locomotor stimulant that elicits dose-dependent increases in ambulation (circling, sniffing, rearing) or stereotypy (head-bobbing, repetitive sniffing), which were noted to be similar to the effects of amfetamines (Baumann *et al.,* 2004; Baumann *et al.,* 2005; Brennan *et al.,* 2007a; Yarosh *et al.,* 2007). These effects were not observed with TFMPP and, when administered in combination with TFMPP, only occurred at high doses (10 mg/kg BZP and TFMPP). Repeated BZP administration produced an increase in hyperactivity, but did not affect stereotypy (Brennan *et al.,* 2007a). It was also shown that repeated BZP exposure resulted in a sensitization and cross-sensitization to metamfetamine (Brennan *et al.,* 2007a). Additional studies in rats further supported potential amfetamine-like behaviour and suggested heightened anxiety with BZP, possibly due to interference in maturation of anxiety-associated forebrain mechanisms (Aitchison and Hughes, 2006). Conditioned place preference tests in rats found BZP possessed rewarding properties mediated by the dopaminergic and serotonergic systems (Meririnne *et al.,* 2006).

In rhesus monkeys, BZP substituted for cocaine in self-administration studies and amfetamine in discrimination studies, but the reinforcing effects of BZP:TFMPP were less than with BZP alone (Fantegrossi *et al.,* 2005). Following cocaine administration sessions with BZP at injected doses of 0.1 and 0.3 mg/kg, the animals exhibited signs of intoxication: involuntary head movements, jaw chattering, bizarre body postures, hyperactivity and 'fly catching'. Because of this, doses above 0.3 mg/kg were not tested, but no behavioural effects were noted at any dose during the amfetamine discrimination study. In addition, self-administered saline sessions suggested BZP had a

fairly long-lasting behavioural effect (Fantegrossi *et al.,* 2005). BZP also substituted for cocaine in rats and self-administration of BZP was acquired rapidly in drug-naïve animals in a dopaminergic-mediated mechanism (Brennan *et al.,* 2007b).

Effects on cognition and behaviour in humans

In a study of former amfetamine addicts, the behavioural effects of BZP, d-amfetamine and a lactose control were compared. The subjective effects of BZP and d-amphetamine were identical and liked by the volunteers (Campbell *et al.,* 1973). There were statistically significant changes in the excitation score, but no difference in the depression score after administration of the drugs. In an additional d-amfetamine comparative study in volunteers with no previous experience of amfetamines, both d-amfetamine and BZP produced a significant improvement in an auditory vigilance test (Bye *et al.,* 1973). No significant changes were found in tests of short duration (tapping rate, hand steadiness and arithmetic), therefore the use of prolonged signal detection was recommended. Subjective effects of BZP (based on the volunteer selecting from a checklist of 41 adjectives) were only detected following a 100 mg dose (7.5 mg in the case of d-amfetamine). Overall, the studies concluded that BZP had a psychomotor stimulant response similar to d-amfetamine but d-amfetamine had an effective potency 10-fold greater than BZP.

More recently, Curly *et al.,* (2013) investigated the effects of an acute dose of BZP, TFMPP or a combination of BZP and TFMPP on the anticipation of reward in a double-blind, placebo-controlled, crossover study using fMRI. An event-related gambling paradigm was completed by healthy controls 90 min after taking an oral dose of either BZP (200 mg), TFMPP (either 50 or 60 mg), BZP + TFMPP (100 + 30 mg) or placebo. After giving BZP, the anticipation of a $4 reward decreased the activation of the inferior frontal gyrus, insula and occipital regions in comparison to placebo. TFMPP increased the activation of the putamen but decreased the activity in the insula relative to placebo. When BZP and TFMPP were given in combination, activation of the rolandic operculum occurred. The magnitude of reward also affected neural correlates. It was proposed that the effects of BZP on dopaminergic circuitry reflect regional changes and appear to increase positive arousal and subsequently reduce the response to uncertainty.

Physiological effects in humans

BZP (50 mg and 100 mg) was found to increase pulse rate, blood pressure (systolic and diastolic) and pupillary dilation (Campbell *et al.,* 1973 and Bye *et al.,* 1973). These effects were comparable to those found with d-amfetamine but no change in pupil size was noted for d-amfetamine by Campbell et al. (1973). Other tests observing the effect of BZP eye-drops on pupil diameter produced results similar to that of tyramine, but different from methoxamine, suggesting an indirect sympathomimetic action (Bye *et al.,* 1973). During the study by Campbell *et al.,* (1973), flushing and sweating were observed after BZP administration.

In a more recent, randomized, double-blind, placebo-controlled study by Lin *et al.,* (2011) the subjective and physiological effects of BZP/TFMPP were investigated in 36 males. Participants were tested before and approximately 2 h after administration of a single dose of placebo or 100/30 mg BZP/TFMPP. The results revealed that BZP/TFMPP increases blood pressure and heart rate and subjective rating scales revealed that BZP/TFMPP has dexamphetamine-like effects. In a related study by Lin *et*

al., (2009) involving 27 females, BZP at 200 mg was again found to increase blood pressure and heart rate and have stimulant effects.

Alansari and Hamilton (2006) reported that a 17-year-old male developed acute renal failure after consuming five BZP tablets and a small amount of alcohol. In the absence of rhabdomyolosis, the authors postulated a causal relationship with BZP toxicity.

Psychological effects in humans

The only published human studies relating to psychological effects are the aforementioned studies by Campbell et al. (1973), Bye et al. (1973) and Lin et al. (2009 and 2011). These showed that BZP had psychomotor stimulant and excitation effects comparable to those of amfetamine but with lower potencies. There were no significant observations in tests assessing tapping rate, hand steadiness or the arithmetic of healthy volunteers (Bye *et al.,* 1973). The studies by Campbell et al. and Bye et al. were set up to investigate acute effects and although follow-up questioning did not reveal any chronic effects, the original tests were not repeated. Through subjective rating scales, the studies by Lin et al. (2009 and 2011) showed BZP/TFMPP increases dysphoria and feelings of self-confidence and in females 200 mg BZP increased euphoria, dysphoria, sociability, and drug liking.

Answers from a questionnaire regarding the use of "party pills" in New Zealand comprised psychological problems such as: trouble sleeping, loss of energy, strange thoughts, mood swings, confusion and irritability (Wilkins *et al.,* 2006). However, none of the participants were confirmed BZP users.

Additional self-reported use from "psychonauts" on the Internet (Erowid and The Lycaeum) described a number of cognitive, mood and mental effects. Most users described BZP as moderately euphoric (but not as much as with MDMA) with a positive effect on mood. Discrete reports mentioned BZP made them much more social, enthusiastic and one user stated it allowed mental tasks to be performed for many hours without becoming fatigued. Conversely, another user stated that their co-ordination and intellectual ability had been negatively affected. Other users reported an on-going feeling of anxiety and uneasiness with positive effects being replaced by irritability. No users mentioned chronic effects.

Overall, users reported both positive and negative effects of BZP on cognition, mood and mental functioning but given the nature of these reports, it is difficult to draw any definitive conclusions.

4.2. Routes of administration and dosage

As BZP 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 in self-reports on the Internet (Erowid and The Lycaeum). Intravenous use is also a possibility (as for amfetamines) 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 and/or TFMPP. Although powders were commonly seen, only one individual (out of 2010) claimed to have injected, two had snorted (insufflated), but none admitted to smoking the drug(s). The typical dose ingested by users appears to be between 50-200 mg of BZP (Sheridan, 2007 and Erowid). This correlates with dosages

used in published trials (Bye *et al.*, 1973 and Campbell *et al.*, 1973). 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

BZP is a metabolite of a previously marketed anti-depressant drug, piberaline (see Section 9). Although piberaline has been studied, direct pharmacokinetic data from animals are not available for BZP, in particular: absorption, distribution, AUC, C_{max}, T_{max} and half-life. However, the effective pharmacological dose (ED_{50}) was 9.3 (+/- 2.7) mg/kg in monkeys, compared to the ED_{50} of amfetamine (0.2 mg/kg) for the procedure used (Fantegrossi *et al.*, 2005).

BZP appears to be metabolised by cytochrome P450 (possibly involving the CYP2D6 iso-enzyme) and catechol-*O*-methyl-transferase (COMT). These systems are prone to genetic polymorphisms, so potential inter-individual and inter-species differences may occur. However, overall, animal and human studies (below) have noted the same metabolites to be present: 4-hydroxy-BZP (4-OH-BZP or *p*-OH-BZP), 3-hydroxy-BZP (3-OH-BZP or *m*-OH-BZP), 4-hydroxy-3-methoxy-BZP, piperazine, benzylamine and *N*-benzylethylenediamine. The 4-hydroxy-BZP, 4-hydroxy-BZP and 4-hydroxy-methoxy-BZP metabolites are also excreted as glucuronic and/or sulfuric acid conjugates in urine (Staack *et al.*, 2002; Maurer *et al.*, 2004; Tsutsumi *et al.*, 2006). Based on metabolism studies in the rat, p-OH-BZP is the major metabolite in Phase I with significant Phase II glucuronide formation (Tsutsumi *et al.*, 2006). Following single intraperitoneal dosing (5 mg/kg BZP), 25% was excreted as *p*-OH-BZP, 2% as *m*-OH-BZP and 6.7% as unchanged BZP - excretion of the parent drug took place within 36 hours (Tsutsumi *et al.*, 2006). Half of the *p*-OH-BZP was excreted as the glucuronide conjugate. The concentration ratio of *p*-OH-BZP to *m*-OH-BZP was 11.6:1 in the first 4 hours which increased to 22.7:1 within 48 hours.

Human studies

Studies with human liver microsomes found BZP is metabolized by the cytochrome P450 iso-enzymes; CYP2D6, CYP1A2 and CYP3A4 (Antia *et al.* 2009a). This supports previous predictions based on animal studies (above). The study found that BZP and TFMPP inhibited each other's metabolism, indicating a potential issue with an interaction of the drugs if used in combination – as well as interactions with other drugs involving cytochrome P450. The following BZP metabolites have been noted in humans: 4-hydroxy-BZP (4-OH-BZP or p-OH-BZP), 3-hydroxy-BZP (3-OH-BZP or m-OH-BZP), 4-hydroxy-3-methoxy-BZP, piperazine, benzylamine and N-benzylethylenediamine. The 4-hydroxy-BZP, 4-hydroxy-BZP and 4-hydroxy-methoxy-BZP metabolites were also found to be excreted as glucuronide and/or sulfate conjugates in urine (Staack *et al.* 2002, Maurer *et al.* 2004, Tsutsumi *et al.* 2005).

Human plasma concentrations of BZP were measured in blood samples taken from healthy adults (n = 7) over 24 h following a 200-mg oral dose of BZP (Antia *et al.* 2009b). Concentrations were found to peak at 262 µg/l (C_{max}) and 75min (T_{max}). Plasma concentrations of the major metabolites of BZP, 4-OH BZP and 3-OH BZP, were found to peak at 7 µg/l (at 60 min) and 13 µg/l (at 75 min), respectively. The elimination half-

life (t1/2) for BZP was found to be 5.5 hs. Clearance (Cl/F) was found to be 99 L/hour. The results of this study indicate that BZP may be detectable in plasma for up to 30 h following an oral dose. Additionally, 4-OH BZP, 3-OH-BZP and predominantly O-sulfate and N-sulfate BZP conjugate metabolites were also found in urine collected over the 24 h (Antia *et al.* 2009b).

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of BZP. However, some clinical human studies have been performed (Section 4.1) and the findings can be combined with non-clinical information.

Overall, BZP appears to produce stimulant and toxic effects similar to amphetamines and other sympathomimetics. TFMPP is commonly used in conjunction with BZP in order to seek the entactogenic effects of MDMA. Adverse effects may occur when BZP is co-ingested with other drugs (in particular MDMA and other serotonergic/dopaminergic compounds), but toxic effects with BZP alone have also been reported. Agitation, tachycardia and seizures have been noted (see Section 6).

6. Adverse reactions in humans

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). It should be noted that only a small proportion of these cases were confirmed by toxicological analysis. The age range was 15-36 years with 1-25 tablets taken (average = 4.5). Other drugs suggested to have been co-ingested were alcohol, cannabis, nitrous oxide, MDMA, LSD and methylphenidate. Symptoms noted were anxiety, vomiting, headache, palpitations, confusion, collapse and seizures; some symptoms had persisted for 24 hours post-ingestion. Of these, vomiting, palpitations and agitation were the most frequently observed. Other clinical features included tachycardia and hypertension with a prolonged QTc in 32% of patients. One patient had hypnonatraemia. Of particular concern to the authors were 14 patients who suffered seizures (described as grand mal type), which reportedly occurred on average 3.9 hours following ingestion (range 0.5-8 hours). Only one of these patients was known to be epileptic. There was no difference in the number of tablets reportedly taken in seizing (4.3) and non-seizing patients (4.55), with one patient having taken 12 tablets before suffering seizures and one patient having only taken 2 tablets. Three cases of severe toxicity are mentioned below.

In a 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. 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, there are a number of Internet-based reports from users (Erowid and The Lycaeum). A range of comments relating to BZP use alone are

presented in brief below relating to the initial years of use. It should be noted that numerous other reports include the combined use of other drugs of abuse. Abridged versions of these reports are as follows:

(i) Nov 2005 (UK?) – First noticed something after 1-1.5 hours. Numerous side-effects for a couple of hours; feeling hot, dry mouth, shaky and mild nausea. Effects not that bad but distracting. Dancing was exhausting, very hot. Stimulant effects kicked in but not in a good MDMA-type way. Trace MDMA-style euphoria after overcoming adverse effects, with following hours of enforced wakefulness.

(ii) Nov 2005 (Ireland) – Felt sweaty, thirsty, shaky, confused and very unpleasant heart palpitations. Feelings of nausea and illness eventually passed into a more pleasant effect which resembled MDMA very strongly but without the "sparkle" typical of phenylethylamines. Superficial effect without feelings of empathy, euphoria typical of pure MDMA. Co-ordination and intellectual ability negatively affected. No jaw clenching unlike with MDMA and amphetamines. Partner reported she found it "quite trippy". Peak lasted 7-8 hours. Throughout experience had on-going feeling of anxiety and uneasiness.

(iii) Feb 2001 (USA?) – Sensory enhancement for the first 2 hours, keeps getting more intense with sensory overload. Makes you feel nauseous, uncomfortable and at some point the drug becomes trippy (eye visuals). Next day had headache. Maybe a lower dose would be better.

(iv) July 2000 (USA?) – 140 mg capsule (oral) took effect after 1.25 hours with mild to medium euphoria. Snorting BZP hurt a lot.

(v) 2000 – Obtained free base liquid and converted to HCl. Took solution, effects became noticeable after 25-35 minutes. Effects peaked at 4 hours and tapered off to 7-8 hours after tolerance built up (tolerance began to be noticeable after 5-8 days of daily use). Effects dropped off much faster. Effects are pleasant, moderately euphoric, made me much more social, unusually happy, enthusiastic and could become absorbed for many hours on abstract mental tasks without becoming fatigued. Also noted: increased heart rate, elevated blood pressure, heavy sweating, weight loss. Overall effects are significantly different from methamphetamine and other similar stimulants; less of a tendency to produce manic behaviour. Tolerance is a problem, having to increase dose from 60 mg to 250 mg. Positive effects replaced by irritability. It is also addictive/self-reinforcing, stopped using it with significant difficulty.

(vi) 2000 – 350 mg (oral) onset of effects at 30-45 minutes with nausea but more pleasant after 1-1.5 hours. Effects like d-amphetamine, peaked at ~2 hours, tapered over next 4-5 hours. Did not experience headaches and all the negative things people have reported. Snorted 75 mg with immediate onset of burning, nice high 10-15 minutes after use. Peak at ~1 hour, slowly tapered off over 3 hours but not baseline after 4 hours. Intravenous use (no dose recorded) caused immediate rush through head/chest area but full trip kicks in and reaches its peak after ~1 hour.

Cases of BZP intoxication in humans

There have been various reports of non-fatal and fatal intoxication where BZP has been found. However, a major problem in investigating the involvement of BZP in hospital admissions and fatalities is the potential lack of laboratory confirmation or diagnosis.

Although numerous methods have been published (see Section 2.G.), BZP is not always included in routine or targeted toxicological analysis or may be detected but not identified as being BZP (Elliott, 2007).

Non-fatal cases

Details of 3 patients in the severe toxicity group were reported by Gee et al. (2005).

Patient 1: (16-year-old female, 4 pills, no alcohol) had a tonic clonic seizure 2.5 hours after her last tablet. Additional seizures were treated with diazepam. GCS 3/15 with intubation. Heart rate (HR) 149 bpm, BP 70/55, blood glucose 5.6 mmol/L, temperature 36^{o}C. After further seizures she had a metabolic and respiratory acidosis. She was transferred to ITU but extubation was possible 12 hours later (GCS 15/15). Laboratory analysis showed BZP and metabolites only. No apparent prolonged adverse effects were reported a week later.

Patient 2: (18-year-old female) had five seizures with metabolic and respiratory acidosis. Transferred to ITU but later extubated with no apparent long-term effects. Laboratory analysis showed BZP only.

Patient 3: (25-year-old male, 2 pills with alcohol and 2 pills following morning) had a tonic seizure 3 hours after last tablet whilst driving a car. HR 170 bpm, BP 148/75, blood glucose 5.4 mmol/L. Drowsy but conversant upon admission. Laboratory analysis showed BZP metabolites and alcohol only.

Comprehensive case details of two further cases of BZP intoxication have also been published (Gee *et al.* 2010). Both cases required prolonged hospital care but survived. A 19-year-old female developed status epilepticus, hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, and renal failure associated with BZP ingestion whilst in police custody. She was transferred to hospital and a plasma BZP concentration of 0.20 mg/L was measured 10 h after being in custody. Benztropine metabolites (patient's medication), nicotine and caffeine were additionally detected in the urine. Case 2 involved a 22-year-old male who developed a similar toxicity from the combined use of BZP and MDMA. Concentrations measured in a blood sample collected 3 h after admission found a BZP concentration of 2.23 mg/L and an MDMA concentration of 1.05 mg/L. A repeat BZP blood level 6 h later was 0.1 mg/L. Gee et al. also reported plasma BZP concentrations in 96 individuals measured on admission to an emergency department over a 2-year period following use of 'party pills' (Gee *et al.* 2008). The concentrations were between 0 and 6.29 mg/L (mean 0.68 mg/L). Patients with concentrations between 0.0 and0.50 mg/L tended to report symptoms of anxiety, palpitations, and vomiting. Agitation, anxiety, and confusion were more frequent above 0.5mg/L. Seizures were associated with levels as low as 0.05 mg/L but increased with higher concentrations and were consistent when plasma levels were above 2.15 mg/L. This took into account the entire cohort of 96 patients who had plasma BZP concentrations measured, whether or not they had co-ingested ethanol.

In May 2006, 7 patients (18-23 years) attended an Accident and Emergency Department in London, UK, from the same nightclub having ingested supposed Ecstasy or amfetamine tablets (4-9 tablets consumed) (Button et al., 2006; Wood et al., 2007). The diamond-shaped tablet ingested by the individuals was found to contain only BZP. Two of the individuals collapsed in the club with witnessed self-terminating grand mal seizures. Upon admission, 5 of the patients exhibited dilated pupils, anxiety, agitation

and tachycardia. After 8 hours of observation and treatment with benzodiazepines, there was no evidence of continued toxicity. Serum samples were analysed in 4 of the patients and revealed BZP concentrations of 1.3, 1.9, 1.9 and 2.5 mg/L (Button et al., 2006). No other piperazines, drugs or alcohol were detected. Clinical information was published for one of the female patients, detailing a seizure in the club, and was agitated, tachycardic (156 bpm), BP 150/51, apyrexial (temperature 35.9oC) and had dilated pupils and a GCS of 15/15. She was discharged after 12 hours (Wood et al., 2007).

The same authors also published instances of three patients presenting to the emergency department after ingesting four tablets thought to be Ecstasy over the course of an evening (Wood *et al.* 2008). It was reported that they presented with dissociative-type symptoms, nausea, and signs consistent with sympathomimetic toxicity. All three improved with conservative management and observation, within 12 h of presentation. TFMPP and BZP were found in serum at concentrations of 263 +/− 5.8 μg/L (range 260–270 μg/l) and 46.7 +/− 15.3 μg/l (range 30–60 μg/l), respectively. No other recreational drugs were detected in the blood and urine samples.

Elsewhere in the UK, between June 2006 and November 2007, BZP was detected in 11 patients, with TFMPP detected in 9 of the cases (Elliott 2007). All cases were confirmed by toxicological analysis. Urine concentrations ranged between 5.21 and 202.7mg/l (BZP) and 0.40–20.66 mg/l (3-TFMPP). In one particular case, BZP and 3-TFMPP was present in urine along with MDMA and methadone. The patient 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. Blood samples were only available in three cases. Case 1 (25-year-old male) serum BZP = 0.17 mg/l. MDMA and citalopram were also present. The patient presented with hyponatraemia, mydriasis and prolonged respiratory depression. Case 2 (24-year-old male) plasma BZP = 0.32 mg/l, 3-TFMPP = 0.08 mg/l. Two BZP tablets were reported to have been taken. Insufficient sample volume was available for additional drug analysis. Case 3 (age/sex not known) plasma BZP = 0.47 mg/l, 3-TFMPP = 0.10 mg/l. No other drug or clinical information was available.

Fatal cases

There have been very few instances of fatalities involving BZP. Six cases have been formally published (Wikström et al., 2004; Balmelli et al., 2001; Elliott 2007; Elliott and Smith, 2008). None involved BZP alone.

In a fatality which occurred in 1999 in Sweden, Wikström et al. (2004) reported the presence of BZP in postmortem blood at a concentration of 1.7 mg/L, in addition to MDMA, MDA and tetrahydrocannabinol (THC). A further fatality in 2002 was mentioned by Wikström et al. (2004) also with a BZP blood concentration of 1.7 mg/L. Amfetamine, MDMA and THC were detected as well. No further details regarding the circumstances of these deaths were described. However, information released to the EMCDDA indicated the decedents were 22-year-old and 24-year-old males, respectively.

Balmelli *et al.,* (2001) published a fatality involving a 23-year-old female in Switzerland. She was admitted to hospital with headache, malaise and somnolence 11 hours after ingestion of BZP and 7 hours after ingestion of MDMA along with large volumes of fluids. She also presented with bradycardia (HR 48 bpm), hypertension (BP

154/95), hypnonatraemia (sodium 115 mmol/L) and a GSC of 6. She seized twice and required intubation. A computerised tomography scan indicated a cerebral oedema and, although the sodium levels returned to normal within 38 hours post-admission, she deteriorated neurologically with increasing tonsillar herniation and died 57 hours after initial presentation. In this case the hypnonatraemia was associated with the intake of fluids after MDMA ingestion, and therefore the specific contribution of BZP is difficult to determine.

Details of three initial fatalities in the UK where BZP was detected are described below (Elliott and Smith 2008):

Case 1: (September 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 postmortem 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: (September 2006) – A 32-year-old male was the driver of vehicle that struck a tree. He was taken to hospital but later died. Comprehensive toxicological analysis of postmortem blood and urine samples found a urinary BZP of 4.88 mg/L, cannabis, benzodiazepines, cocaine, diltiazem, amfetamine, MDMA and ketamine. No alcohol was detected. Blood analysis showed BZP (<0.50 mg/L), ketamine, MDMA (0.54 mg/L), amfetamine, diazepam, cocaine, cyclizine and atracurium. No alcohol was found. There was insufficient sample volume for measurement of the additional drugs present. Note: The atracurium and possibly cyclizine and diazepam were present as part of medical treatment. Also, in the UK, diltiazem is sometimes found as an adulterant in illicit cocaine (Elliott 2007).

Case 3: (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 postmortem 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 was reported to have been found in a further 19 fatalities between 2007 and 2010 and are summarized in the table below (Elliott 2011). BZP and 3-TFMPP were detected together in each case, suggesting possible concomitant ingestion. Of the cases, six involved a mechanical cause of death (e.g. RTA, hanging), six cases were likely due to other drug use (e.g. heroin, methadone) and seven cases had no obvious alternative cause of death. However, due to the presence of other drugs, medical history, and case circumstances, the actual significance of BZP or 3-TFMPP was unclear. In fact the highest post mortem blood concentration (3.20 mg/L BZP) was found where the manner of death was hanging. However, in 2012 one fatality involved a 47 year old male with a history of hypertension was found unresponsive and was pronounced dead upon arrival at hospital. A post-mortem femoral blood BZP concentration of 20.4 mg/L was found, with no contribution from alcohol or other drugs (Elliott and Evans 2014).

Case No.	Other cause?	Deceased age/sex	PM Urine piperazines	PM Blood piperazines	Otherdrugs detected
1	Hanging	34 yr male	Not available	BZP 0.68 mg/L 3-TFMPP 0.04 mg/L	Not available
2	Hanging	23 yr male	BZP 3-TFMPP	BZP 3.20 mg/L	Cocaine MDMA Levamisole Cannabis Alcohol
3	Pedestrian RTA	33 yr male	BZP 3-TFMPP	BZP <0.3 mg/L 3-TFMPP <0.03 mg/L	Methadone Alcohol
4	Heroin	30 yr male	Not available	BZP 0.68 mg/L 3-TFMPP 0.04 mg/L	Morphine Benzodiazepines
5	None	19 yr male	BZP 3-TFMPP	BZP 0.69 mg/L 3-TFMPP 0.08 mg/L	Lignocaine
6	None	26 yr male	BZP 3-TFMPP	BZP 1.91 mg/L 3-TFMPP 0.07 mg/L	Cannabis Cocaine Levamisole Lignocaine Diazepam Alcohol
7	Methadone	35 yr male	BZP 3-TFMPP	None detected	Methadone Diazepam
8	Heroin	25 yr male	BZP 3-TFMPP	None detected	Morphine Cannabis Cocaine Trimethoprim Alcohol
9	None	36 yr male	BZP 3-TFMPP	BZP <0.3 mg/L	Lansoprazole Amphetamine
10	RTA	22 yr male	BZP 3-TFMPP	BZP 1.44 mg/L 3-TFMPP 0.20 mg/L	Alcohol Cannabis
11	Hanging	33 yr male	BZP 3-TFMPP	BZP 1.12 mg/L 3-TFMPP 0.30 mg/L	Ketamine Alcohol
12	None	38 yr male	BZP 3-TFMPP	None detected	Cannabis Venlafaxine Paracetamol
13	Heroin	45 yr male	BZP 3-TFMPP	None detected	Cannabis Diazepam Olanzapine Amitriptyline Morphine
14	None	38 yr male	BZP 3-TFMPP	None detected	Paracetamol Promethazine Venlafaxine
15	Heroin	33 yr male	BZP 3-TFMPP	3-TFMPP <0.03 mg/L	Cocaine Morphine Levamisole Alcohol
16	Hanging	25 yr male	BZP 3-TFMPP	None detected	Cannabis Methadone Diazepam Citalopram Alcohol
17	Heroin	27 yr male	BZP 3-TFMPP	None detected	Morphine
18	None	23 yr male	BZP 3-TFMPP	None detected	Amitriptyline Diazepam Methadone Cannabis

Case No.	Other cause?	Deceased age/sex	PM Urine piperazines	PM Blood piperazines	Otherdrugs detected
					Ketamine Morphine Sildenafil
19	None	48 yr male	BZP 3-TFMPP	3-TFMPP <0.03 mg/L	Alcohol

7. Dependence potential

See 8 (below)

8. Abuse potential

There have been few studies regarding the dependence/abuse potential of BZP with no specific studies in humans. However, following the study by Campbell et al. of the administration of BZP in former addicts, it was suggested that BZP is liable to abuse (Campbell *et al.* 1973). 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". Although some anecdotal reports in users on the Internet mention addiction and dependence, there are no clinical studies to support this. Nonetheless, animal studies found that BZP possessed rewarding properties, reinforcing effects and substituted for cocaine, amphetamine and S(+)-MDMA in self-administration and discrimination studies (Meririnne *et al.*, 2006; Fantegrossi *et al.*, 2005; Yarosh *et al.*, 2007). Therefore, it appears that BZP could possess an abuse and dependence potential.

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

BZP was synthesised in the early 1940s by the Burroughs Wellcome Company (Buck and Balztly, 1947). It is often reported that BZP was originally developed as a potential anthelminthic for the treatment of intestinal parasitic worms in livestock, but was not licensed as it was found to be relatively ineffective and caused adverse effects such as seizures in mammals. However, no published or unpublished work confirm this.

In the 1980s, BZP was used by the EGYT (now EGIS) pharmaceutical company in Hungary to manufacture the active substance piberaline (1-(phenylmethyl)-4-(2-pyridinylcarbonyl)-piperazine) otherwise known as 1-benzyl-4-picolinoylpiperazine or EGYT-475 (Magyar 1987). This was originally marketed as an anti-depressant under the proprietary name Trelibet®. Piberaline is metabolised to BZP, which may have been partly responsible for its activity. Trelibet® was later withdrawn.

BZP is sometimes described in the news media as a "worming agent", but this is misleading since it has never been licensed as an anthelminthic drug (King and Nutt, 2007). Although BZP may find use on a small scale for research purposes, as far as is known it has no current human or veterinary pharmaceutical use in any country. BZP is not, and has not been, the subject of a marketing authorization.

10. Listing on the WHO Model List of Essential Medicines

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

11. Marketing authorizations (as a medicine)

BZP has never been marketed as a medicine.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

12. Industrial use

BZP has no industrial use.

13. Non-medical use, abuse and dependence

BZP use and seized material has been reported in numerous countries including USA, New Zealand, Australia and many in Europe (Denmark, Finland, Belgium, UK, Sweden, Portugal, Italy, France, Netherlands, Lithuania, Norway, Greece, Malta, Spain and Germany).

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

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

BZP 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. TFMPP) or other drugs. Consequently, poly-drug 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 drugs is a common finding in both non-fatal and fatal cases. Only a discrete collection of hospital admissions were toxicologically proven to solely involve BZP.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

15. Licit production, consumption and international trade

Not applicable. Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

16. Illicit manufacture and traffic and related information

Refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

Not applicable in relation to affecting impact of medical use.

For non-medical use in one country, Wilkins et al repeated in 2009 their 2006 survey of BZP use in New Zealand (Wilkins and Sweetsur 2013). They reported that prevalence of BZP use amongst the general population fell from 15.3% in 2006 to 3.2% in 2009. The most common reasons described for stopping BZP use in 2008 were 'it's illegal now' (43%), 'just experimenting' (26%), 'don't know where to get it now it's illegal' (24%) and 'bad hangover effect' (18%). Three per cent of the general population had used any new legal high in 2009. Use of BZP declined among frequent methamphetamine users from 32% in 2006 to 7% in 2010; among frequent Ecstasy users from 65% in 2006 to 11% in 2010; and among frequent injecting drug users from 30% in 2007 to 20% in 2010. The use of new legal highs in 2010 was lower than the former use of BZP in 2006. The overall level of legal high use was lower following the prohibition of BZP with unpleasant side-effects and the prohibition being reported to have contributed to a decline in BZP use.

18. Current and past national controls

European Union: controlled across Member States as recommended by the Council of the European Union following a risk assessment by the EMCDDA.
USA: controlled (Schedule I)
Australia: controlled
Japan: controlled (as a narcotic)
New Zealand: controlled
Thailand: controlled

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

None

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This critical review with updates is based on the Technical Annexes of the Risk Assessment of BZP for the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) produced by Dr Simon Elliott and Dr Les King and the publication; Elliott SP (2011). Current awareness of piperazines: pharmacology and toxicology. Drug Test Analysis 3: 430-438.

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Annex 1
Report on WHO Questionnai9re for Review of Psychoactive Substances for the 36th ECDD Evaluation of N-benzylpiperazine (BZP)

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR). A total of 69 Member States answered the questionnaire for N-benzylpiperazine (BZP). Of these, only 32 respondents (AMR 5, EMR 1, EUR 21, SEAR 1, WPR 4) had information on this substance.

LEGITIMATE USE

None reported that BZP was currently authorized or is in the process of being authorized/registered as a medical product in their country. Seven respondents stated that this substance was used for purposes such as research, intermediate in pharmaceuticals and as reference analytical standard. There was no stated use for animal/veterinary care

HARMFUL USE

Eighteen respondents confirmed that there was recreational/harmful use of BZP; common routes of administration were stated as oral by 15 and as oral/ injecting/ inhaling/sniffing by one. Twelve respondents stated this was obtained via trafficking, 2 stated trafficking plus clandestine manufacturing and one reported diversion. The common formulations of BZP available were reported as tablet, powder/tablet, powder, powder/tablet/liquid and tablet/liquid by 9,4,2,2,and 1 respondents respectively. Three respondents also mention the link between BZP and ecstasy. 8 reported only club use while 2 stated use in clubs and among general population and one stated that it was only used by the general population. One overdose death is reported in 2012. Three respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by BZP. These include seizures, vomiting, headache, palpitations, tachycardia, hypertension, poor appetite, nausea, anxiety, insomnia, strange thoughts, mood swings, confusion, irritability and tremors.

CONTROL

Of those with information on this substance, 30 reported that BZP was controlled under legislation that was intended to regulate its availability -24 under “controlled substance act”, 2 under “medicines law”, 2 under “generic legislation” and 2 under “other” laws. Only 1 respondent stated that there were challenges with the implementation of this legislation. On illicit activities involving BZP, two respondents reported clandestine manufacture; one the synthesis of the product itself. Fifteen reported trafficking, four reported diversion and 10 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	5,797 (11)	4,789 (12)
Total quantity seized (kg)	74.11 (8)	48.24 (7)
Total quantity seized (ampoules)	12 (1)	
Total quantity seized (tablets/pills)	251 (5)	546 (3)
Total quantity seized (other)		273 blotters (1)

IMPACT OF SCHEDULING

Twenty-eight respondents reported that if BZP was placed under international control, they would have the laboratory capacity to identify the substance. It has no reported medical use.