N-benzylpiperazine (BZP)
Pre-Review Report

Expert Committee on Drug Dependence
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N-benzylpiperazine (BZP)
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35th ECDD (2012) Agenda item 5.3a

N-benzylpiperazine (BZP)
SUMMARY .......................................................................................................................... 7

1. Substance identification ........................................................................................................ 8
   A. International Nonproprietary Name (INN) .................................................................. 8
   B. Chemical Abstract Service (CAS) Registry Number ..................................................... 8
   C. Other Names .................................................................................................................. 8
   D. Trade Names .................................................................................................................. 8
   E. Street Names .................................................................................................................. 8
   F. Physical properties: ......................................................................................................... 8
   G. WHO Review History: ................................................................................................... 8

2. Chemistry ............................................................................................................................... 9
   A. Chemical Name ............................................................................................................... 9
   B. Chemical Structure ......................................................................................................... 9
   C. Stereoisomers .................................................................................................................. 9
   D. Synthesis ......................................................................................................................... 9
   E. Chemical description ...................................................................................................... 9
   F. Chemical properties ...................................................................................................... 10
   G. Chemical identification .................................................................................................. 10

3. Ease of convertibility into controlled substances ................................................................. 10

4. General pharmacology ........................................................................................................ 10
   4.1. Pharmacodynamics .................................................................................................... 10
   4.2. Routes of Administration ............................................................................................ 14
   4.3. Pharmacokinetics ........................................................................................................ 14

5. Toxicology ............................................................................................................................ 15

6. Adverse reactions in humans ............................................................................................... 16

7. Dependence potential .......................................................................................................... 21

8. Abuse potential ..................................................................................................................... 21

9. Therapeutic applications, extent of therapeutic use and epidemiology of medical use ........ 21

10. Listing on the WHO Model List of Essential Medicines .................................................. 21

11. Marketing authorizations (as a medicine) ......................................................................... 22

12. Industrial use ...................................................................................................................... 22

13. Non-medical use, abuse and dependence .......................................................................... 22

35th ECDD (2012) Agenda item 5.3a

N-benzylpiperazine (BZP)

15. Licit production, consumption and international trade ............................................. 23
16. Illicit manufacture and traffic and related information ............................................. 23
17. Current international controls and their impact ......................................................... 23
18. Current and past national controls ............................................................................. 23
19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance .................................................................................................................. 24

References ......................................................................................................................... 25

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 Scandinavia 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 the substance as “legal Ecstasy” or as a “legal high”. Such products typically contain other piperazine derivatives in variable quantities. Toxic effects have been reported in users (agitation, tachycardia and seizures) with associated hospital admissions, but cases involving BZP alone are rare. Although BZP 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 BZP in these instances. Animal studies have indicated both an abuse and dependence potential for BZP but human clinical studies to support this are limited.
Pre-review of N-benzylpiperazine (BZP)

1. Substance identification

A. International Nonproprietary Name (INN)
   Not applicable.

B. Chemical Abstract Service (CAS) Registry Number
   2759-28-6 (free base)
   5321-63-1 (dihydrochloride salt)
   72878-35-4 (mono-hydrochloride salt)

C. Other Names
   Benzylpiperazine, BZP, 1-benzylpiperazine, N-benzylpiperazine, 1-benzyl-1,4-diazacyclohexane,

D. Trade Names
   None.

E. Street Names

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

F. Physical properties:
   The 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:
   Several reports suggest a large misuse of BZP over the last years, especially in the EU and countries like New Zealand. Following a risk assessment by Europol and the EMCDDA in 2007, a Council Decision of 2008 introduced controls on BZP in the European Union. 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 BZP 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-benzylpiperazine
CA Index Name: 1-benzylpiperazine

B. Chemical Structure

Free base:

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\text{\begin{center}
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\end{center}}
\]

Molecular Formula: \( \text{C}_{11}\text{H}_{16}\text{N}_{2} \)
Molecular Weight: 176.26 g/mol (free base); 249.19 g/mol (dihydrochloride salt)
Melting point: 17-20 °C (base); 289-292 °C (dihydrochloride salt)
Boiling point: 143-146 °C (base)
Fusion point: > 123 °C (base)

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) can be converted to the monohydrochloride salt but monohydrochloride can also be produced from the commercially-available dihydrochloride, phosphate or citrate salts. 1,4-Dibenzylpiperazine (DBZP) may be produced as a side-product during the process and has been found in some BZP-containing tablets.

E. Chemical description

Piperazine is a heterocyclic compound containing four carbon atoms and two of nitrogen at 1,4 position (also called 1,4-hexahydropyrazine). It is normally produced as the dihydrochloride salt. Like the 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 phenylcyclidine and with 1-phenylethylamine and its derivatives (King et al., 1996).
F. Chemical properties

BZP free base is a liquid and hydrochloride salt is a white solid soluble in water, alcohol, glycerol, and glycols.

G. Chemical identification

Analysis of solid samples by gas-chromatography and mass spectrometry (GCMS) is straightforward, and derivatisation is not required. Bishop et al. (2005) used capillary electrophoresis to separate six piperazine derivatives. Collections of analytical data (GCMS, IR, TLC and immunoassay) have been published (Aunan and Ely, 1999; Maurer, 2004 and Kenyon, 2007). The mass spectrum has peaks at (m/z) = 91 (base peak); 134, 56, 176 and 65. BZP does not give a colouration with Marquis or Scott’s field tests, but does give a positive reaction with Nitroprusside reagent.

There is some cross-reactivity with commercially available urine immunoassay tests for methamphetamine. According to Kenyon (2007), BZP reacts with the Syva ‘RapidTest d.a.u.’ for methamphetamine at a concentration of 10μg/ml, but does not react, even at 100μg/ml, with the Syva ‘RapidTest d.a.u.’ for amphetamine or the Acon test for methamphetamine. Methods for the identification and quantification of BZP in body fluids have been provided by de Boer et al. (2001), Staack et al. (2002), Peters et al. (2003), Inoue et al. (2004), Nordgren et al. (2005), Tsutsumi et al. (2005), Button et al. (2007), Elliott and Smith (2008), Antia et al. (2010) and Wohlfarth et al. (2010). Most of these rely either on GCMS or liquid chromatography coupled with mass spectrometry (LC-MS).

3. Ease of convertibility into controlled substances

BZP is not readily converted into controlled substances.

4. General pharmacology

4.1. Pharmacodynamics

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, methamphetamine or amphetamine.

Specifically, with regard to the adrenergic system, rabbit studies found BZP to be an α2-adrenoreceptor antagonist thereby inhibiting the pre-synaptic negative feedback mechanism (yohimbine-like and tyramine-life effect) (Magyar et al., 1986 and Magyar 1987). However, an in vitro study using cortical slices of rat brain showed no presynaptic α2-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 et al., 1986, Magyar 1987, Szucks et al., 1987). Tekes et al.
(1987) also showed BZP released NA as well as inhibiting 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 particular 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\textsubscript{2} receptors and both inhibition of 5-HT uptake and 5-HT\textsubscript{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 release of newly-synthesised DA (Oberlander et al., 1979).

More recent studies in rats found BZP caused the release of a dopamine transporter substrate (\textsuperscript{3}(H)MPP\textsuperscript{+}) \textit{in vitro} and produced an \textit{in vivo} increase in extracellular DA and 5-HT: the latter only at a high dosage (Baumann et al., 2004, 2005). This was noted to be reminiscent of methamphetamine. TFMPP was found to be a selective releaser of 5-HT transporter substrate (\textsuperscript{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 of MDMA. At a higher dose of 10 mg/kg BZP:TFMPP increased DA to a higher degree than the substances 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, 2005).

During the animal studies described above, BZP has been observed to produce seizures, particularly at high doses with TFMPP in rats (Baumann et al., 2004, 2005). Hyperthermia and muscle contraction was also observed during rat studies (Tekes et al., 1987 and Magyar et al., 1986).

It is possible that BZP might provide some protection against the neurotoxic effects of MDMA. Hashimoto et al., (1992) found that administration of BZP reduced the levels of 5-HT and 5-hydroxyindole acetic acid in the cerebral cortex of rats that had previously been injected with 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 elicited dose-dependent increases in ambulation (circling, sniffing, rearing) and stereotypy (head-bobbing, repetitive sniffing), which were noted to be similar to the effects of amphetamines (Baumann et al., 2004, 2005; Brennan et al., 2007, 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). Repeated BZP administration produced an increase in hyperactivity, but did not affect stereotypy (Brennan et al., 2007). It was also shown that repeated BZP exposure resulted in a sensitization and cross-sensitization to methamphetamine (Brennan et al., 2007). Additional rat studies
further supported potential amphetamine-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 and amphetamine in self-administration and discrimination studies, respectively, but the reinforcing effects of BZP:TFMPP were less than BZP alone (Fantegrossi et al., 2005). Following cocaine 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 amphetamine 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 substance-naive animals in a dopaminergic-mediated mechanism (Brennan et al., 2007).

**Effects on cognition and behavior in humans**

In a study of former amphetamine misusers, the behavioural effects of BZP, d-amphetamine 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 substances. In an additional d-amphetamine comparative study in volunteers with no previous experience of amphetamines, both d-amphetamine 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 check list of 41 adjectives) were only detected following a 100 mg dose (7.5 mg in the case of d-amphetamine). Overall, the studies concluded that BZP had a psychomotor stimulant response similar to d-amphetamine but d-amphetamine had an effective potency 10-fold higher.

**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). The effects were comparable to d-amphetamine but no change in pupil size was noted for d-amphetamine by Campbell et al. (1973). Other tests observing the effect of BZP eye-drops on pupil diameter produced results similar to tyramine, but different from methoxamine, suggesting an indirect sympathomimetic action (Bye et al., 1973). During the study by Campbell et al., flushing and sweating were observed after BZP administration.

Alansari and Hamilton (2006) reported that a 17 year old male developed acute renal failure after consuming a small amount of alcohol and five BZP tablets. In the absence of rhabdomyolysis, the authors postulated a causal relationship with BZP toxicity. 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. In a related study involving 27 females, BZP at 200 mg was again found to increase blood pressure and heart rate and have stimulant effects, increased euphoria, dysphoria, sociability and substance liking (Lin et al., 2009).

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**
The published human studies relating to psychological effects by Campbell et al. and Bye et al. in 1973 showed BZP had psychomotor stimulant and excitation effects comparable to amphetamine but with lower potency. There were no significant observations in tests assessing tapping rate, hand steadiness and arithmetic of healthy volunteers (Bye et al., 1973). Both studies concerned acute effects and although follow-up questioning did not reveal any chronic effects, the original tests were not repeated. As mentioned above, additional studies by Lin et al, indicated increased dysphoria and feelings of self-confidence in males and increased euphoria, dysphoria and sociability in females (Lin et al., 2011 and 2009, respectively).

A questionnaire regarding “party pills” in New Zealand mentioned 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-reports from users on the Internet (Erowid and The Lycaeum) described a number of cognitive, mood and mental effects. Most users described BZP as moderately euphoric (not as much as 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 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 report both positive and negative effects of BZP on cognition, mood and mental functioning but 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 BZP, there would be an expected interaction with other substances that affect the monoamine systems. In particular, other serotonin and dopamine releasing agents and re-uptake inhibitors are likely to exacerbate the effects of BZP and vice versa. In the case of serotonergic compounds, the development of a serotonin syndrome is possible. In addition to prescription medicines such as most antidepressants, concomitant use of MDMA, other amphetamines and cocaine could cause significant problems (Gee et al., 2005, Fantegrossi et al., 2005). Self-reporting users\(^1\) indicate poly-substance use is common as an intended adjunct to BZP use and many mention the additional use of these substances as well as GHB and other piperazines (especially TFMPP and mCPP). Based on studies of BZP and TFMPP in rats, Baumann et al. (2004) suggested the potential for dangerous consequences if the substances were taken in combination.

A further potential issue, as mentioned in the study by Gee et al, (2005), indicated that users presenting to the Emergency Department appeared to have taken a number of BZP tablets, reportedly due to a slow onset of action following oral use.

4.2. Routes of Administration

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 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 2010) 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 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, piberaline (see Section 7). Although piberaline has been studied, direct pharmacokinetic data from animals are not available for BZP: in particular, absorption, distribution, AUC, C\(_{\text{max}}\), T\(_{\text{max}}\) and half-life. However, the effective pharmacological dose ED\(_{50}\) was 9.3 (+/- 2.7) mg/kg in monkeys, which compared to the ED\(_{50}\) of amphetamine (0.2 mg/kg) for the procedure used (Fantegrossi et al., 2005).

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\(^1\) http://www.erowid.org (http://www.erowid.org/experiences/subs/exp_Piperazines_BZP.shtml) and http://leda.lycaeum.org/ (http://leda.lycaeum.org/?Table=Trips&Ref_ID=415)
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 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 glucuronide and/or sulfate conjugates in urine (Staack et al., 2002; Maurer et al., 2004; Tsutsumi et al., 2006). Based on metabolic studies in the rat, 4-hydroxy-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 substance 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 in the 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., 2009). The substances inhibited each other’s metabolism, further indicating a potential issue with an interaction of the substances if used in combination – as well as interactions with other substances involving cytochrome P450. The postulation that BZP follows the same metabolic fate as in rats is evidenced by the involvement of cytochrome P450 and catechol-O-methyl-transferase as well as the appearance in human urine of the metabolites p-OH-BZP, m-OH-BZP, 4-hydroxy-3-methoxy-BZP, piperazine, benzylamine and N-benzylethylenediamine (Staack et al., 2002, Maurer et al., 2004). It is proposed that like the rat, p-OH-BZP is the major Phase I metabolite and, although glucuronide formation occurs, sulfation may be the major Phase II process as this is the most common route for phenolic compounds in man (Staack et al., 2002 and Tsutsumi et al., 2006).

Human plasma concentrations of BZP were measured in blood samples taken from healthy adults (n = 7) over 24 hours following a 200-mg oral dose of BZP. Concentrations were found to peak at 262 μg/L (Cmax) and 75 minutes (Tmax). 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 minutes) and 13 μg/L (at 75 minutes) respectively. The elimination half-life (t(1/2)) for BZP was found to be 5.5 hours. 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 hours 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 hours (Antia et al., 2009).

**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 and the findings can be combined with non-clinical information.
6. **Adverse reactions in humans**

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 are likely to occur when BZP is co-ingested with other substances (in particular MDMA and other serotonergic/dopaminergic compounds), but toxic effects with BZP alone have been reported. Agitation, tachycardia and seizures may occur.

In Europe, use of BZP was first reported in Sweden in 1999 (Wikström et al., 2004). Continued surveillance by these authors led to BZP being found in 56 individual cases submitted to the National Laboratory (1999-2003) and included substance abusers, inmates, substance treatment patients, drivers and a fatality. In the vast majority of instances, other common substances of abuse were also detected (MDMA, cannabis, amphetamine, morphine, ‘kat’ and benzodiazepines). Blood concentrations in users ranged between 0.02 and 1.2 mg/l (Wikström et al., 2004).

A study in New Zealand of clinical admissions associated with party pill use (April-September 2005) reported 61 patients on 80 occasions attended the Emergency Department with adverse effects (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 substances 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 hyponatraemia. 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 for 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 the New Zealand Household survey (Wilkins et al., 2006), 2,010 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. A range of comments relating to BZP use alone are presented in brief below. It should be noted that numerous other reports include the combined use of other substances of abuse.

(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 substance 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 dependence producing/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 (Peters et al., 2003; Inoue et al., 2004; Nordgren et al., 2005; de Boer et al., 2001), 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 °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.

In May 2006, 7 patients (18-23 years) attended an accident and Emergency Department in London, UK, from the same nightclub having ingested purported ecstasy or amphetamine 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) (10). No other piperazines, substances 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 35.9 °C) and had dilated pupils and a GCS of 15/15. She was discharged after 12 hours (Wood et al., 2007).

The occurrence of grand mal seizures in some individuals who had taken BZP is a notable feature of the published clinical reports (Gee et. al., 2005; Wood et al., 2007) and is also confirmed in some studies on rats (Baumann et al., 2004, 2005). However, according to Sheridan (2007), despite widespread use of BZP in New Zealand, there have been no other reports of this problem. The impact of BZP-based party pills on the Auckland City (New Zealand) emergency department overdose database was reported by Theron et al., (2007). They concluded that BZP represented less than 2% of entries. In an Australian study, it was noted that only half the respondents described the effects of ‘party pills’ as good; negative effects included palpitations, dizziness, insomnia, dehydration and after-effects that could last from hours to days. Of 1,043 people, only six had sought medical attention because of the effects of BZP (Nicholson, 2006).

Between June 2006-November 2007, BZP was detected in 9 patients elsewhere in the UK, with TFMPP also detected in 8 of the cases (Elliott, 2007 and Elliott, 2011). All
cases were confirmed by toxicological analysis as summarised below. Blood/serum samples were only available in 2 cases.

**Case 1**: May 2006 - 14 year old male; Urine BZP = 83.21 mg/l. No clinical information.

**Case 2**: June 2006 - 32 year old male; Urine BZP = 35.75 mg/l, 3-TFMPP = 0.40 mg/l. No clinical information.

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

**Case 4**: December 2006 - 26 year old male; Urine BZP ~ 39.87 mg/l, 3-TFMPP ~ 12.13 mg/l. MDMA and methadone also present. A 26 year old male 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 5**: 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 6**: May 2007 - 25 year old male; Urine BZP ~ 10.6 mg/l. Serum BZP = 0.17 mg/l. MDMA and citalopram also present. Patient presented with hypnonatraemia, mydriasis and prolonged respiratory depression.

**Case 7**: August 2007 - 19 year old male; Urine BZP ~ 202.7 mg/l, 3-TFMPP ~ 20.66 mg/l. MDMA and amphetamine also present. No clinical information.

**Case 8**: November 2007 – age/sex not known; Urine BZP and 3-TFMPP (not measured). 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; Urine BZP and 3-TFMPP (not measured). No other substance or clinical information available.

**Fatal cases:**
There have been relatively few instances of fatalities involving BZP. 25 cases have been formally published (Wikström et al., 2004; Balmelli et al., 2001, Elliott, 2007, Elliott and Smith, 2008 and Elliott, 2011). None involved BZP alone.

In a fatality which occurred in 1999 in Sweden, Wikström et al. (2004) reported the presence of BZP in post mortem 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. Amphetamine, 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 deceased 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), hyponatraemia (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 hyponatraemia was associated with the intake of fluids after MDMA ingestion, and therefore the specific contribution of BZP is difficult to determine.

Details of 3 fatalities in the UK where BZP was detected are set out 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 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: (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 post mortem blood and urine samples found a urinary BZP of 4.88 mg/l, cannabis, benzodiazepines, cocaine, diltiazem, amphetamine, MDMA and ketamine. No alcohol was detected. Blood analysis showed BZP (<0.50 mg/l), ketamine, MDMA (0.54 mg/l), amphetamine, diazepam, cocaine, cyclizine and atracurium. No alcohol was found. There was insufficient sample volume for measurement of the additional substances 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 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 concentration (3.20 mg/L BZP) was 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 BZP (and TFMPP 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 BZP to specific effects or outcome.
7. Dependence potential

Although some anecdotal reports from 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 and amphetamine in self-administration and discrimination studies (Meririnne et al., 2006; Fantegrossi et al., 2005). Therefore, it appears that BZP could possess an abuse and dependence potential.

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. (1973) of the administration of BZP in people with dependence in the past, it was suggested that BZP is liable to abuse. In the New Zealand Household survey (Wilkins et al., 2006; Wilkins et al., 2007), found that approximately one in seven had used ‘legal party pills’ in the last year and of those, ‘one in 45 (2.2 %) were classified as dependent on legal party pills’.

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

BZP was synthesised in the early 1940’s by the Burroughs Wellcome Company (Buck and Balztly, 1947). It is often stated 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, there does not appear to be any published or unpublished work to confirm this.

In the 1980’s, 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 metabolises to BZP, which may have been partly responsible for its activity. Trelibet® was later withdrawn.

BZP is sometimes described in the news media as “worming agent”, but this is misleading since it has never been licensed as an anthelminthic medicine (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 authorisation.

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.

12. **Industrial use**

   BZP has no industrial use.

13. **Non-medical use, abuse and dependence**

   Based on the report of the WHO questionnaire for review of psychoactive substances for the 35th ECDD (annexe 1), 10 countries of the 59 countries responding, reported on the use of BZP in a harmful way and 5 countries reported on the extent of the harmful use. 5 countries indicated tablets as the most common way how BZP is abused. 2 countries reported the abuse in the form of capsules and 2 countries reported that loose powder also occurs. When abused, BZP is administered orally and it is also, inhaled, smoked or snorted.

   The typical dose ingested by misusers 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).

   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).

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) 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. TFMPP) 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. Only a discrete collection of hospital admissions were toxicologically proven to solely involve BZP.
15. **Licit production, consumption and international trade**

   Not applicable.

16. **Illicit manufacture and traffic and related information**

   No specific data.

17. **Current international controls and their impact**

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

18. **Current and past national controls**

   For the most recent data see also results of the WHO questionnaire for review of psychoactive substances for the 35th ECDD conducted during the year 2008 (Annex 1). 14 countries reported that BZP is controlled under legislation that is intended to regulate availability of substances of abuse.

   **European Union:** Recommended for control by EMCDDA but not widely controlled at present (Feb 2007), except for:
   - Belgium,
   - Denmark,
   - Estonia,
   - France,
   - Greece,
   - Italy,
   - Lithuania,
   - Malta,
   - Netherlands,
   - Spain, and
   - Sweden.

   **USA:** controlled (Schedule I).
   **Australia:** controlled.
   **Japan:** controlled (as a narcotic).
   **New Zealand:** controlled.

   The substance was classified as a Schedule I controlled substance in the United States in 2002, following a report by the DEA which incorrectly stated that BZP was 10 to 20 times more potent than amphetamine, when in fact BZP is ten times less potent than dexamphetamine. The DEA subsequently admitted this mistake, but nevertheless retained the Schedule 1 classification (Wikipedia).

   BZP is banned in all Australian states. Victoria, the last state in which it was legal, changed its classification on September 1 2006. This is the date BZP and piperazine
analogs became illegal in the federal schedules which are now enacted by all Australian states and territories. BZP is also a banned substance in Japan, along with TFMPP. Both Australia and Japan admit that their scheduling decisions were made primarily in response to the Schedule 1 classification given to BZP in the USA, although some instances of BZP use had been reported by law enforcement authorities in both countries.

BZP is also banned in Greece, Italy, Malta, Denmark and Sweden.

Piperazine and salts of piperazine are classified as "Prescription Only Medicines" in the UK. Any products containing salts of piperazine would be licensable under the Medicines Act and consequently anyone manufacturing and supplying it legally must hold the relevant licenses to do so. BZP is not a salt of piperazine, but mislabelling of BZP products as containing "piperazine blend" have resulted in some prosecutions of suppliers in the UK by the Medicines and Healthcare Products Regulatory Agency, though to this date there has not been a successful prosecution in the UK for the sale of BZP, so its legal status remains uncertain. Although sale is regulated, possession of BZP is still legal.

For now, BZP and other analogous piperazines are legal and uncontrolled in many countries such as Canada and Ireland. They are not controlled under any UN convention, so the compounds themselves are legal throughout most of the world, although in most countries their use is restricted to pharmaceutical manufacturing and recreational use is unknown.

Benzylpiperazine has, however, been the subject of a European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) risk assessment. The results were published in June 2007. The report concluded that the use of BZP can lead to medical problems even if the long term effects are still unknown. Taking this concession as a basis, the European Commission has decided to ask the Council to place BZP under control. On 4 March 2008, BZP was placed under control in the EU.

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.

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

No data.
References

This pre-review 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.


ANNEX 1: WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD – Evaluation of N-benzylpiperazine (BZP)

The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for N-benzylpiperazine (BZP) by 60 countries.

LEGITIMATE USE

No country out of 59 reported authorized BZP as a medical or veterinary product. It is also not legitimated by any reported country for other legitimate use. Only two countries out of 59 reported authorized BZP for technical use. Australia authorized BZP for forensic analysis and in the USA it is commonly used industrially as an intermediate in chemical synthesis.

Two countries, Australia and Brunei, indicated that they import the substance.

ABUSE

Of the 59 countries responding, 10 countries reported on the use of BZP in a harmful way and 5 countries reported on the extent of the harmful use. 5 countries indicated tablets as the most common way how BZP is abused. 2 countries reported the abuse in the form of capsules and 2 countries reported that loose powder also occurs. When abused, BZP is administered orally and it is also, inhaled, smoked or snorted.

The use of tablets is reported from Australia, Cyprus and the Czech Republic, Germany, and the Republic of Korea reported beside the use of tablets also the use of capsules and loose powder.

Other reports on the extent of the abuse are reported in Denmark, Germany, the Republic of Korea and the USA. Also 4 countries reported on the extent of public health or social problems associated with the harmful use of BZP. At least one instance of death that has officially been linked with the use of BZP is reported in Australia. Germany reported a range of adverse reactions such as vomiting, headache, palpitations, poor appetite, stomach pain/nausea, anxiety, insomnia, strange thoughts, mood swings, confusion, irritability and tremors. Further Germany indicated that BZP has been found in post mortem samples, however, the extent to which BZP was implicated in the deaths is not known: in all cases other substances or other circumstances were involved. There is no evidence that BZP use leads to serious social harm. However, an important caveat is that the lack of evidence makes drawing any strong conclusions difficult. The Republic of Korea reported that nausea, vomiting, hallucination, high blood pressure, insomnia, mental diseases and toxic nephropathy also occur. The USA reported that BZP induces increased heart rate, blood pressure and body temperature. In case of chronic abuse it can cause irregular heartbeats and can cause the occurrence of delusion, hallucinations, and paranoia.

CONTROL
14 countries reported that BZP is controlled under legislation that is intended to regulate availability of substances of abuse. Mauritius reported to have a proposal to regulate the control of the substance. The Netherlands reported that they will regulate it on a short term (based on European legislation).

In Norway it is not controlled under legislation that intends to regulate availability of the abuse of BZP. However Norway has decided that BZP is to be regarded as covered by the Act on Medical Products which contains control measures.

6 countries have tracked illicit activities involving the substance. Clandestine manufacturing and diversion are not reported. Smuggling is reported 2 times and other illicit activities are also reported twice.

8 countries reported on the quantity of the seizures. The seizures vary from 3 tablets to thousands of tablets. The biggest reported seizures are from the USA with 74 seizures, 16 g of powder, and 160855 tablets. Other seizures are reported in Cyprus with 900 tablets, Mauritius with 500 tablets and Malta with 162 tablets. Smaller seizures are reported in Denmark and Greece. Germany finds it not possible to state the total number of seizures of BZP or the total quantity seized. Seizures of BZP occurred only in a few isolated cases involving small and minute quantities. Further seizures were not statistically recorded in all cases in Germany. In Australia the quantity of seizures is unknown.

**IMPACT OF SCHEDULING**

10 countries reported that if BZP is placed under more strict international control, the availability for medical use will be affected. Armenia doesn't have any official information. Australia reported that BZP is treated as a prohibited substance for which there is no approved therapeutic use. The manufacturing, possession, sale or use of BZP is prohibited by law except when it is required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities. In Bangladesh BZP is not authorized as a medial or veterinary product. In Cyprus a decree to include BZP as a controlled substance is undergoing legal vetting. In Japan BZP has already been controlled as narcotics under the Narcotics and Psychotropic Substances Control Law since October 2003. According to Norwegian legislation medicinal products, for personal use, may not be imported from countries outside the EEA (European Economic Area). When importing (for personal use) from countries in the EEA, the customs officer may ask the importer to present a prescription or some other kind of documentation that the product is intended for medical use. In Portugal it is under study to be listed as one of the controlled substance under national laws. In the Republic of Korea BZP is classified as a psychotropic substance as of 2008. Finally Tuvalu reported that under the dangerous drugs acts, no person should import/export any of these substances without authorization by the Ministry of Health.

There are no reports on how a transfer will impact the medical availability.

**Brand Name**

No information

**Technical Use**
- Forensic analysis
- Industrially as an intermediate in chemical synthesis