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EMCDDA

RISK ASSESSMENTS

Report on the risk assessment of BZP
in the framework of the Council decision
on new psychoactive substances





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for Drugs and Drug Addiction

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EMCDDA project leader

Dr Roumen Sedefov

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- the members of the extended Scientific Committee of the EMCDDA; the advisers to the Scientific Committee and the invited external experts who took part in the risk assessment meeting;
- Dr Leslie A. King and Dr Simon Elliott for preparing the technical review on the pharmacotoxicological, sociological and criminological evidence and public health risks of 1-benzylpiperazine (BZP); and the former for his invaluable advice during the risk assessment meeting.

Foreword

The European Union has responded to concerns over the use of the stimulant drug BZP by assessing the health and social risks of the substance and, consequently, subjecting it to control measures across the Member States. The decision of the Council, defining BZP as a new psychoactive substance which is to be controlled, was adopted in the final stage of a three-step process — information exchange/early warning, risk assessment and control of new psychoactive substances — designed to respond to potentially threatening new psychoactive drugs in the EU. Such a concrete result at a political level confirms the effectiveness of the rapid-response mechanism, provided by the Council decision on the information exchange, risk assessment and control of new psychoactive substances.

This Council decision allows the EU institutions and Member States to act on all new and potentially threatening narcotic and psychotropic drugs (natural and synthetic alike) which appear on the European drug scene. Under the terms of the decision, the EMCDDA and Europol, in collaboration with their respective networks — Reitox and Europol national units, and the European Medicines Agency (EMA) — play a central role in detecting new psychoactive drugs, assessing their characteristics and paving the way for eventual control measures. The legal instrument also provides strong encouragement for further cooperation between the EMCDDA and its institutional partners, involved in the risk assessment process.

Furthermore, the decision enhances the capacity of the EU institutions and the Member States to detect and monitor new trends. New forms of drug use are usually adopted by a few individuals, among small groups or in particular regions and social settings. BZP, however, was widely and legally available in some countries from retail chemical suppliers and products containing BZP have been openly sold through Internet sites or retail outlets, providing for a higher potential for spread than other new substances previously encountered in Europe. Therefore, keeping our ear to the ground and picking up on new substances and trends is a central part of our work at the EMCDDA, to ensure that problems are detected before they become major health or social threats.

This publication presents the findings of the formal risk assessment on BZP, produced in 2007 by the Scientific Committee of the EMCDDA, with participation of additional experts from the European Commission, Europol and the EMEA. The risk assessment report, which was submitted to the European Commission and the Council of the European Union on 31 May 2007, examines the health and social risks of the drug, as well as information on international trafficking and the involvement of organised crime. Furthermore, the report considers the potential implications for placing the drug under control in the EU. On the basis of this report — and on the initiative of the European Commission — on 3 March 2008, the Council decided that BZP is to be subject to control measures.

I would like to thank the members of the EMCDDA Scientific Committee, the European Commission, Europol, the EMEA and EMCDDA experts who participated in the risk assessment process for BZP, for the high quality of work carried out. The resulting report is a valuable contribution at European level, which gives clear support to political decision-making. Furthermore, I would like to recognise the excellent work done in preparing the risk assessment by the networks of the EMCDDA, Europol and the EMEA — the Reitox national focal points, Europol national units and the national competent authorities responsible for medicinal products — who played an essential role in collecting and providing national data, thus completing this truly multidisciplinary effort.

Wolfgang Götz

Director, EMCDDA

Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
AUC	area under curve (concentration time)
BP	blood pressure (systolic/diastolic)
BZP	1-benzylpiperazine
C_{max}	maximum concentration
DA	dopamine
DBZP	1,4-dibenzylpiperazine
DEA	Drug Enforcement Administration
ED₅₀	median effective dose
EWS	early warning system (EMCDDA–Europol)
GCMS	gas chromatography-mass spectrometry
GCS	Glasgow Coma Scale
GHB	gamma-hydroxybutyrate
HR (bpm)	heart rate (beats per minute)
IR	infra-red spectroscopy
ITU	Intensive Therapy Unit
mCPP	1-(3-chlorophenyl)piperazine
MDMA	3,4-methylenedioxymethamphetamine (ecstasy)
MeOPP	1-(4-methoxyphenyl)piperazine
MPP	4-methylphenylpiperazine
NA	noradrenaline
QTc	time interval in electrocardiogram
TFMPP	1-(3-trifluoromethylphenyl)piperazine
TLC	thin-layer chromatography
T_{max}	time to maximum concentration

Introduction

The risk assessment of BZP is the first to be implemented under the terms of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, which replaced the 1997 joint action on new synthetic drugs. Furthermore, BZP is the first piperazine derivative to be risk assessed by the extended Scientific Committee of the EMCDDA.

The appearance and spread of various piperazines is a significant and new phenomenon, given the fact that a vast majority of the reported psychoactive substances since the establishment of the early warning system in 1997, belong to two 'traditional' chemical groups — phenethylamines and tryptamines. It is worth noting that of the nine new synthetic drugs that underwent risk assessment between 1997 and 2005, under the terms of the 1997 joint action on new synthetic drugs, all six substances that were subsequently controlled at EU level are phenethylamines.

The (aryl-substituted) piperazines are a group of chemicals which includes, amongst others, 1-benzylpiperazine (BZP), 1-(3-chlorophenyl)piperazine (mCPP), m-trifluoromethylphenylpiperazine (TFMPP). All of these have been individually notified through the early warning system, but the different members of this chemical group are often marketed and used in various combinations, usually in the form of 'party pills'.

The specific scientific risk assessment of BZP has been extremely difficult, due to the fact that there is very little similarity to the compounds which were previously risk assessed by the EMCDDA Scientific Committee. Furthermore, most of the data concerning BZP use ('party pills') originate from New Zealand, a country with a distinctive drug situation, which may not translate to the European context. However, in preparing and carrying out the risk assessment of BZP, the extended Scientific Committee of the EMCDDA and the involved institutions — Europol, the EMEA and the European Commission — as well as partners from Member States, demonstrated that the system set up by the decision is operational and able to abide by the stipulated strict deadlines.

The decision does not provide for a range of options for control of new psychoactive substances to be considered. The option for control that is available at European Union level is for the Member States to submit the new psychotropic drug BZP to control measures, as provided under their legislation, by virtue of their obligations under the 1971 United Nations Convention on Psychotropic Substances. Therefore, even though the extended Scientific Committee of the EMCDDA unanimously agreed that there is a need to control BZP, it was aware that such a measure could have contradictory effects. On the one hand, it could limit the potential for expansion of the supply and use of BZP by facilitating the capacity for the detection and monitoring of illegal manufacturing of and trafficking in BZP, and international law enforcement cooperation. However, on the other hand, it could create an illegal market in BZP with an increased risk of criminal activity, or even lead to its replacement with other psychoactive substances, which may also have public health consequences. The Committee also recommended that if a decision is made to place BZP under control, this should not inhibit the gathering and dissemination of accurate information on BZP to users and to relevant professionals.

Based on the lessons learnt during the seven years of implementation of the 1997 joint action on new synthetic drugs and the experiences gathered in implementing Council Decision 2005/387/JHA between 2005 and 2008, including the risk assessment of BZP (2007), 'Guidelines for the risk assessment on new synthetic drugs', which were drafted in 1999, now need to be adapted and revised. Furthermore, to address some of the current data limitations in the risk assessment process, the Scientific Committee recognises that a numerical scoring system could be a useful working tool in the preparation of the actual risk assessment, although it may not constitute a formal part of the risk assessment report. Such a system could be used as a trigger to focus the discussion on relevant items.

It is our firm belief that, given the complexity of the work, the risk assessment report presents unambiguous and, as far as possible, evidence-based advice to the Council and the Commission. However, taking into account the nature of the new drugs phenomenon, any risk assessment on a substance at such an early stage of knowledge and scientific evidence, would inevitably have an element of inconclusiveness. If time and resources are available, some of the data limitations for the risk assessment exercise could be partly addressed through future research.

Finally, we would like to thank all our colleagues from the extended Scientific Committee for their hard work. Furthermore, we would like to express our gratitude to the two external experts — Dr Leslie A. King and Dr Simon Elliott and to the EMCDDA staff: in particular, Dr Roumen Sedefov (project leader of this report), Paul Griffiths, Brendan Hughes, Anabela Almeida and Deborah Olszewski, who worked hard before, during and after the meeting to finalise the reports, in order to provide detailed and precise conclusions and to ensure a speedy completion of the process; and Fiona Brown, who coordinated this publication. We hope that all these efforts will be appreciated by those to whom this report is addressed.

Dr Michael Farrell,

Chairperson of the EMCDDA's Scientific Committee

Prof. Henk Garretsen,

Chairperson of the EMCDDA's Scientific Committee (2005–08)

Council decision

Council Decision 2008/206/JHA of 3 March 2008 on defining 1-benzylpiperazine (BZP) as a new psychoactive substance which is to be made subject to control measures and criminal provisions

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on European Union,

Having regard to the Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances ⁽¹⁾, and in particular Article 8(3) thereof,

Having regard to the initiative of the Commission,

After consultation of the European Parliament,

Whereas:

- (1) A Risk Assessment Report on 1-benzylpiperazine (BZP) was drawn up on the basis of Decision 2005/387/JHA by a special session of the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction and subsequently submitted to the Council and the Commission on 31 May 2007.
- (2) BZP is a synthetic substance. It was first reported in the European Union in 1999. Like amphetamine and methamphetamine, BZP is a central nervous system stimulant, but with a much lower potency (around 10 % of that of d-amphetamine). The metabolism of BZP may be affected by genetic polymorphisms in enzyme systems leading to a wide inter-individual susceptibility to the effects of BZP. There is also a potential for interactions with other drugs, but overall there is a lack of human pharmacokinetic data.
- (3) In some Member States BZP is legally available from retail chemical suppliers; for recreational purposes it is sold as tablets and capsules via Internet sites or in some Member States in 'smart/herbal shops'. On the illicit drugs market, BZP may also be sold/bought as the popular drug ecstasy.

(1) OJ L 127, 20.5.2005, p. 32.

- (4) Thirteen Member States and one third State (Norway) have reported seizures of BZP in powder, capsules or tablets, ranging from one capsule/tablet up to 64 900 tablets. There is little information that may suggest large-scale synthesis, processing or distribution of BZP, and the involvement of organised crime.
- (5) BZP has no established and acknowledged medical value; there are no known licensed medicinal products containing BZP in the European Union.
- (6) BZP is currently not under assessment and has not been under assessment by the UN system. In five Member States, BZP is subjected to control measures and criminal penalties as provided under their legislation by virtue of their obligations under the 1961 or 1971 UN Conventions. Two Member States apply control measures to BZP under their medicines legislation.
- (7) BZP has been found in post mortem samples. However, the extent to which BZP was implicated in the deaths is not known as in all cases other substances or other circumstances were involved.
- (8) The Risk Assessment Report on BZP reveals a lack of conclusive scientific evidence on the overall risks of BZP. However, due to its stimulant properties, risk to health, the lack of medical benefits and following the precautionary principle, there is a need to control BZP, but the control measures should be appropriate to the relatively low risks of the substance.
- (9) Placing 1-benzylpiperazine under control may help avoid problems in international law enforcement and judicial cooperation,

HAS DECIDED AS FOLLOWS:

Article 1

Member States shall take the necessary measures, in accordance with their national law, to submit 1-benzylpiperazine (also known as 1-benzyl-1,4-diazacyclohexane, N-benzylpiperazine or — less precisely — as benzylpiperazine or BZP) to control measures proportionate to the risks of the substance, and criminal penalties, as provided for under their legislation complying with their obligations under the 1971 United Nations Convention on Psychotropic Substances.

Article 2

This Decision shall be published in the *Official Journal of the European Union*.

It shall take effect on the day following its publication.

Done at Brussels, 3 March 2008.

*For the Council
The President
J. Podobnik*

Chapter 1

Risk assessment report of a new psychoactive substance: 1-benzylpiperazine (BZP)

Introduction

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ⁽²⁾ (hereinafter the ‘Decision’) establishes a mechanism for the rapid exchange of information on new psychoactive substances that may pose public health and social threats, including the involvement of organised crime, thus allowing European Union institutions and Member States to act on all new narcotic and psychotropic substances ⁽³⁾ that appear on the European Union drug scene. The Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if applicable, measures in the Member States for the control of narcotic and psychotropic substances ⁽⁴⁾ can be applied to the new substances.

In compliance with the provisions of Article 5 of the Decision, the EMCDDA and Europol submitted on 23 February 2007 to the Council, the Commission and the European Medicines Agency (EMA) a joint report on the new psychoactive substance 1-benzylpiperazine (BZP) (6645/07 Cordroque 17). Based on the joint report’s recommendations, and in accordance with Article 6.1 of the Decision, on 23 March 2007, the Council formally requested that ‘the risks, including the health and social risks, caused by the use of, the manufacture of, and traffic in, a new psychoactive substance, the involvement of organised crime and possible consequences of control measures, be assessed’ for BZP.

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

⁽²⁾ According to the definition provided by the Council Decision, a ‘new psychoactive substance’ means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; ‘new narcotic drug’ means a substance in pure form or in a preparation, that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; ‘new psychotropic drug’ means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

⁽⁴⁾ In compliance with the provisions of the 1961 UN Single Convention on Narcotic Drugs and the 1971 UN Convention on Psychotropic Substances.

In accordance with Article 6.2, the meeting to assess the risks of BZP was convened under the auspices of the EMCDDA Scientific Committee with the participation of experts from the Commission, Europol and the EMEA. The meeting took place on 30 May 2007 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMEA.

The Scientific Committee considered the following documents:

- (i) Risk assessment: 1-benzylpiperazine BZP — Technical Annexes (A, B, C and D) as set out in the 'Guidelines for the risk assessment of new synthetic drugs', EMCDDA, 1999;
- (ii) Europol-EMCDDA joint report on a new psychoactive substance: 1-benzylpiperazine (BZP);
- (iii) scientific articles, official reports, media articles and grey literature;
- (iv) Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances.

In compliance with Article 6.4 on completion of the risk assessment, a report (hereinafter 'risk assessment report') was drawn up by the Scientific Committee. The risk assessment report presents an analysis of the scientific and law enforcement information available, and reflects all opinions held by the members of the Committee.

The risk assessment report is hereby submitted to the Commission and Council, within the stipulated period of 12 weeks from the date of the notification by the General Secretariat of the Council.

Physical and chemical description of 1-benzylpiperazine (BZP) and its mechanisms of action, including its medical value

The new psychotropic substance 1-benzylpiperazine is a synthetic product. Also known as 1-benzyl-1,4-diazacyclohexane, N-benzylpiperazine or, less precisely, as benzylpiperazine or just BZP, it has no stereoisomers. BZP is normally manufactured as the dihydrochloride salt. The base is a pale, slightly yellowish-green liquid; the hydrochloride salt is a white solid. Like other arylpiperazines (e.g. mCPP), it is not chemically 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.

BZP is usually available as either tablets or capsules, but loose powders also occur, some of which could have been sourced from legitimate chemical suppliers. Solutions of BZP have been encountered less frequently. Although BZP does not give a coloured reaction with commonly-used field test reagents, laboratory analysis using gas-chromatography coupled to mass spectrometry (GC/MS) is straightforward. Collections of analytical data have been published. There is some cross-reactivity with commercially-available urine immunoassay tests for methamphetamine.

BZP is a derivative of piperazine. The latter has been widely used for many years as an anthelmintic drug, e.g. in the treatment of intestinal roundworm infestations. Piperazine itself has no psychoactive properties. However, BZP was never developed as a potential anthelmintic drug, despite widespread statements to this effect in the scientific literature. Other myths surrounding BZP include suggestions that it is of herbal origin and that it 'contains' piperazine. It has no current pharmaceutical or other commercial use, although BZP may find use on a small scale for research purposes. There are no known licensed medicinal products containing BZP in the European Union.

BZP was investigated by the Burroughs Wellcome Company as a potential antidepressant drug. This work was abandoned in the early 1970s when it was found that BZP was a central nervous system (CNS) stimulant with similar properties to amphetamine. 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). This was

marketed in Hungary as an antidepressant under the proprietary name Trelibet®, which was later withdrawn. Piberaline metabolises to BZP, which may have been partly responsible for its activity.

Chemical precursors that are used for the manufacture of BZP

BZP can be synthesised by reacting piperazine monohydrochloride with benzyl chloride. This process is easier than the manufacture of synthetic drugs such as amphetamine or MDMA, but nevertheless requires basic chemical laboratory facilities.

Piperazine monohydrochloride is easily produced from the commercially-available piperazine dihydrochloride, phosphate or citrate salts. Piperazine and its salts can be purchased without restriction in some countries from retail chemical suppliers, and it can also be extracted from medicinal products. For example, in the UK, one proprietary preparation which can be obtained without prescription contains 4 g of piperazine phosphate in a standard therapeutic dose: a quantity that is theoretically convertible into over 3 g BZP, i.e. enough for around 30 doses.

The other essential precursor — benzyl chloride — is used in a number of large-scale industrial chemical processes; it is readily and cheaply available.

Health risks associated with BZP

Like amphetamine and methamphetamine, BZP is a CNS stimulant, but with a much lower potency (around 10 % of that of d-amphetamine). A typical dose of BZP is about 100 mg. Controlled trials have shown that the subjective effects of BZP are similar to those of amphetamine.

Animal studies found that BZP can substitute for cocaine and amphetamine, in self-administration and discrimination studies. There are limited human data on the abuse and dependence potential. The studies that do exist suggest a similarity to amphetamine. Therefore, it appears that BZP could possess an abuse and dependence potential, but the evidence available is not sufficiently strong to draw a firm conclusion on this point.

One animal study has shown that BZP increases the extracellular concentration of dopamine, serotonin and to a lesser extent, noradrenaline. As with some other drugs, BZP appears to be metabolised by cytochrome P450 (the data suggest the involvement of the CYP2D6 isoenzyme) and catechol-O-methyl-transferase (COMT). Metabolism may therefore be affected by genetic polymorphism, which might result in an increased risk of toxic effects for CYP2D6 poor metabolisers. There is also a potential for interactions with other drugs, but overall there is a lack of human pharmacokinetic data.

There is an absence of standard safety pharmacology and toxicology data. Only a few direct studies have been made on the physiological properties of BZP in humans, and nothing has been published on the effects of BZP on specific organ systems. Much of the available information derives from indirect sources, either from studies of Trelibet®, from self-reports of users on Internet sites, from clinical observation of intoxicated patients or from post-mortem material. Many of these latter 'case reports' involve polydrug use and therefore suffer from problems of interpretation.

Many BZP tablets and capsules also contain TFMPP (1-(3-trifluoromethyl-phenyl) piperazine). Furthermore, surveys in New Zealand have shown that most users consume BZP with alcohol as well as other psychoactive substances.

Apart from the risks inherent in any substance that causes tachycardia, raised blood pressure, agitation and hyperactivity, BZP can lead to other medical problems. Animal studies have shown that BZP, in combination with TFMPP, can produce seizures at high doses in rats. Clinical reports from patients who have consumed BZP suggest an association with grand mal seizures, even in those without any previous history of seizures. However, this finding is based on a very small number of cases. No data exist that allow the relationship between dose and adverse effects to be quantified.

Users have reported a range of adverse reactions such as vomiting, headache, palpitations, poor appetite, stomach pains/nausea, anxiety, insomnia, strange thoughts, mood swings, confusion, irritability and tremors. Some of these occurred in the 'comedown' period, and some persisted for 24 hours after use.

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 drugs or other circumstances were involved.

In New Zealand, a country with the greatest experience of BZP use, a recent household survey of 'legal party pills', which contain BZP and TFMPP, reported very low levels of dependency ⁽⁵⁾. The drug situation in New Zealand is distinctive, and may not translate to the European context. Although some anecdotal reports from users on the Internet mention addiction and dependence, there are no clinical studies to support this.

Social risks associated with BZP

Overall, there is a lack of robust data to allow comment on the social risk associated with BZP to be made with confidence.

BZP is largely sold as tablets and capsules, often via Internet sites, some of which are based in the European Union. Otherwise, in some Member States BZP can be purchased in 'smart shops' and 'legal high' stalls at music festivals. Specific names for these products include 'Jax', 'A2', 'pep twisted', 'pep love' and many others; generic terms for BZP-containing tablets and capsules include 'legal XTC', 'pep pills', 'herbal highs', 'social tonics' and 'party pills'. It is believed that many of these BZP-containing products originated in New Zealand, where a large market has developed for this substance. Many users will therefore have a clear idea that they are purchasing a distinct substance — BZP. Moreover, on the illegal drugs market in the European Union, BZP may also be sold/bought as the popular drug ecstasy.

Users of BZP are, therefore, not a homogeneous group. It is likely that they include individuals who would by choice not use illegal drugs, but also users of ecstasy and amphetamine/methamphetamine. It is a general point that legally available substances that can be legitimately promoted may have a greater potential for spread than controlled substances.

There have been no reports of violence or money laundering in connection with wholesale production and distribution of BZP. Furthermore, there is no specific evidence of negative social consequences or linking the use of BZP to disorderly conduct, acquisitive crime or violence.

As with any drug use, lack of scientific and objective information can contribute

⁽⁵⁾ The survey consisted of a random national household sample of 2 010 people aged 13–45 years old. One in 45 (2.2 %) of those who had used 'legal party pills' in the last year (15.3 % of the total sample) were classified as dependent by scoring greater than four on the combined five questions of the short dependency scale (SDS) (Wilkins et al., 2006). However, dependence measured in surveys using this kind of approach is not equivalent to clinical assessment and, therefore, conclusions should be drawn with caution.

towards increased risks. Firstly, inaccurate media coverage may promote diffusion by encouraging young people to try BZP. And secondly, official dissemination of inaccurate information may undermine the credibility of the official sources.

To address social consequences of BZP use is to infer cause–effect relationships, which are not justified by the data. A conservative interpretation of this absence of evidence might indicate that the use of BZP leads to very limited social harms.

Information on the level of involvement of organised crime and information on seizures and/or detections by the authorities and the manufacture of BZP

Although BZP is not a controlled substance in most Member States, the tablets look like ‘ecstasy’, usually bearing typical logos, so it is inevitable that they would be seized by police and customs authorities. The first report of BZP in the European Union was made in 1999 in Sweden, but it did not become more widespread as a recreational drug in the rest of Europe until the second half of 2004.

Since May 2007, BZP has been reported in seizures in 13 Member States (Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Malta, the Netherlands, Portugal, Spain, Sweden and the United Kingdom) and Norway. But most reported only a few cases and many were of small amounts. In addition, BZP was found in collected samples in several Member States (e.g. Austria, the Netherlands and the UK) either through formal tablet analysis schemes or by ad-hoc test purchases.

The two countries with both the largest number of seizures and the largest amounts were Sweden and the United Kingdom. Since 2000, Sweden has reported 118 police seizures of BZP, many of which were in the south of the country. Almost half of the cases consisted of white, beige or yellow powders; the remainder were capsules in a variety of colours and, since 2003, tablets in various colours. Several seizures of powders were made by Swedish customs over the past five years, the largest being 23 kg, together with parts of a tableting machine. By far the largest single seizure of BZP dosage units in Europe occurred in London in July 2006 when 64 900 tablets — together with firearms — were recovered from a vehicle. Two seizures involving a total of 5 379 tablets were made in Scotland in late 2006. The ‘Mitsubishi’ and ‘Smiley face’ design were common logos on these

tablets, suggesting that BZP is partly sold and purchased as 'ecstasy'.

Apart from the large seizures noted above, there has been no other evidence of the involvement of organised crime. In Europe, BZP is widely available from retail chemical suppliers and there seems to be no need for illicit synthesis. A small-scale 'laboratory' was discovered in Germany in 2005 where both solids and liquids containing BZP were recovered. There has been no other direct evidence that BZP has been synthesised in the European Union, although it is possible that tableting/encapsulating operations may exist.

Information on any assessment of BZP in the United Nations system

The World Health Organization (WHO) is the specialised UN agency designated for the evaluation of medical, scientific and public health aspects of psychoactive substances under the 1961 and 1971 UN Conventions. WHO informed the EMCDDA that 1-benzylpiperazine (BZP) is currently not under assessment and has not been under assessment by the UN system.

Control measures that are applicable to BZP

In 20 Member States and in Norway, 1-benzylpiperazine is not a subject of national drug control or medicinal legislation.

In four Member States — Belgium, Denmark, Greece and Malta — BZP is subjected to control measures and criminal penalties as provided under their legislation, by virtue of their obligations under the 1961 or 1971 UN Conventions. In Sweden, BZP is a subject of control under a specific law on goods dangerous to health.

In Belgium, on 18 November 2004, BZP was included in Article 2, Section 2 of the Royal Decree on Psychotropic Substances. This section includes, amongst others, mCPP, PMMA, 2C-I, ketamine and GHB. In Denmark, as of 3 December 2005, BZP is listed in Table B of the Executive Order 698/1993 on Euphoric Substances. This table lists substances used for medical and scientific purposes with substantial controls (cocaine, MDMA, amphetamines, methadone). In Malta, as of 16 June 2006, BZP is controlled as a psychotropic substance under Part A of the Third Schedule of the Medical and Kindred Professions Ordinance (Chapter 31). Substances controlled in the same list include MDMA, PMA and 2C-T-2. In Greece, since 18 February 2003,

BZP is classified in Table A of Law 1729/87. This table lists substances for which handling is the exclusive right of the State (cannabis, heroin, LSD, MDMA).

In Sweden, since 1 March 2003, BZP is controlled under the Act on the Prohibition of Certain Goods Dangerous to Health (1999:58). The Act lists substances under control but which are not classified as 'narcotics'. Other substances under the same control level are MBDB, BDB, DOC, 5-MeO-DMT, GBL, 1,4-BD, etc.

In two Member States — the Netherlands and Spain — BZP falls under the medicines legislation. In the Netherlands, BZP in pharmaceutical form is considered to be a medicinal product and is, therefore, controlled under medicinal products legislation, whereby production and trade require a licence. Breach of this may be punished by up to six years of imprisonment. Other substances under the same control include: mCPP, ketamine, Ephedra extracts and methylene.

In Spain, BZP is considered a substance which, 'when administered to human beings, modifies physiological functions'. Therefore, BZP (when intended for use in humans), is considered as an active substance, as defined by the applicable Spanish legislation (Law 29/2006). Substances having such status undergo certain control measures — they are inspected by the pharmaceutical inspectorate and customs, manufacturers, traders, importers or distributors working with this substance must notify annually their activities to the Spanish Medicines Agency. Furthermore, authorities can exert enforcement actions on these companies, including suspension of activities.

Options for control and the possible consequences of the control measures

Under Article 9.1 of Council Decision 2005/387/JHA, the option for control that is available at European Union level is for the Member States to submit the new psychotropic drug BZP to control measures and criminal penalties, as provided under their legislation, by virtue of their obligations under the 1971 United Nations Convention on Psychotropic Substances.

There are no specific European studies on possible consequences of such control measures. However, the Committee considers that, if pursued, this option could:

- (i) facilitate the capacity for the detection and monitoring of illegal manufacturing of and trafficking in BZP and the subsequent international law enforcement cooperation;
- (ii) limit the potential for expansion of the supply and use of BZP;
- (iii) have no significant impact on pharmaceutical and chemical industries;
- (iv) create an illegal market in BZP with the increased risk of criminal activity;
- (v) lead to replacement with other psychoactive substances which may have public health consequences.

Summary findings

BZP is a synthetic substance; it was first reported in the European Union in 1999. In some Member States BZP is legally available from retail chemical suppliers; for recreational purposes it is sold as tablets and capsules via Internet sites or in some Member States in 'smart/legal high shops'. Many BZP products also contain the psychoactive substance TFMP (1-(3-trifluoromethyl-phenyl)piperazine). On the illegal drugs market, BZP may also be sold/bought as the popular drug 'ecstasy'.

Thirteen Member States and one Third State (Norway) have reported seizures of BZP in powder, capsules or tablets, ranging from 1 capsule/tablet up to 64 900 tablets. There is little information that may suggest large-scale synthesis, processing or distribution of BZP, and a role of organised crime.

Like amphetamine and methamphetamine, BZP is a CNS stimulant, but with a much lower potency (around 10 % of that of d-amphetamine). The metabolism of BZP may be affected by genetic polymorphisms in enzyme systems leading to a wide inter-individual susceptibility to the effects of BZP. There is also a potential for interactions with other drugs, but overall there is a lack of human pharmacokinetic data.

Users have reported a range of adverse reactions such as vomiting, headache, palpitations, poor appetite, stomach pains/nausea, anxiety, insomnia, strange thoughts, mood swings, confusion, irritability and tremors. Although based on a small number of cases, clinical reports from patients who have consumed BZP suggest an association with grand mal seizures.

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 drugs 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.

BZP has no established and acknowledged medical value; there are no known licensed medicinal products containing BZP in the European Union.

BZP is currently not under assessment and has not been under assessment by the UN system.

In five Member States, BZP is subjected to control measures and criminal penalties as provided under their legislation, by virtue of their obligations under the 1961 or 1971 UN Conventions or equivalent. Two Member States apply control measures to BZP under their medicines legislation.

Recommendations

The overall conclusion of the Committee was that due to its stimulant properties, risk to health and the lack of medical benefits, there is a need to control BZP. However, the Committee felt that the control measures should be appropriate to the relatively low risks of the substance.

There is no evidence that the substance is safe for human consumption. As consumers are not protected, an argument must therefore exist that drug control legislation may be appropriate. Such control would avoid problems in international law enforcement and judicial cooperation. However, it should also be noted that the evidence for harms arising from this drug are not strong and control measures could lead to increasing criminal involvement and possible replacement with other substances.

The Committee recommended that if a decision is made to place BZP under control, this should not inhibit the gathering and dissemination of accurate information on BZP to users and to relevant professionals.

Many of the questions posed by the lack of evidence on the health and social risks of BZP could be answered through relatively simple and inexpensive research. A strong conclusion of the Committee was that further studies are needed, especially in respect to potential neurotoxicity and social consequences.

Lisbon, 30 May 2007

Chapter 2

Europol–EMCDDA joint report on BZP

Europol–EMCDDA joint report on a new psychoactive substance: 1-benzylpiperazine (BZP) – in accordance with Article 5 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances

In December 2006, the EMCDDA and Europol examined the available information on a new psychoactive substance, 1-benzylpiperazine (BZP) through a joint assessment based upon the following criteria: (1) the amount of the material seized; (2) evidence of organised crime involvement; (3) evidence of international trafficking; (4) analogy with better-studied compounds; (5) evidence of the potential for further (rapid) spread; and (6) evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information collected on BZP satisfies at least criteria 1, 3, 5 and 6. The two organisations, therefore, concluded that sufficient information has been accumulated to merit the production of a joint report on BZP as stipulated by Article 5.1 of the Decision. Accordingly, the Reitox NFPs, the ENUs, the EMEA and WHO have been formally requested to provide the relevant information within six weeks from the date of the request, i.e. by 23 January 2007 at the latest.

The resulting joint report on BZP was submitted to the Council, the Commission and the European Medicines Agency (EMA) on 23 February 2007. The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in BZP, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA.

The full text of the joint report can be found at:

<http://www.emcdda.europa.eu/publications/risk-assessments/bzp>

Chapter 3

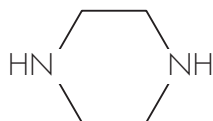
Review of the pharmacotoxicological data on 1-benzylpiperazine (BZP) (6)

Dr Leslie A. King and Dr Simon Elliott

Introduction: The piperazine family

Piperazine (Figure 1) is widely used as an anthelmintic drug in the treatment of intestinal roundworms. Many derivatives of piperazine have been developed as pharmaceutical agents or intermediates. They fall into two main structural groups: the 1-benzylpiperazines and the 1-phenylpiperazines, both of which may be further substituted. The former group includes the numerous diphenylmethylpiperazines, which have found use as antihistamine/anti-emetic drugs. An example here is cyclizine (1-diphenylmethyl-4-methylpiperazine).

Figure 1. Chemical structure of piperazine



Among the phenylpiperazines, at least one (1-(3-chlorophenyl)piperazine: mCPP) is used as a starting product for the manufacture of several antidepressant drugs, e.g. trazodone and nefazodone (Europol-EMCDDA, 2006).

Both benzyl- and phenylpiperazines have been reported as drugs of misuse in Europe and elsewhere. These include mCPP and its positional isomer pCPP, MeOPP (1-(4-methoxyphenyl)piperazine), MPP (4-methylphenylpiperazine), FPP (1-(4-fluorophenyl)piperazine), TFMPP (1-(3-trifluoromethylphenyl)piperazine), 1-benzyl-4-methylpiperazine, MDBP (1-(3,4-methylenedioxybenzyl)piperazine) and BZP (1-benzylpiperazine). Apart from the diphenylmethylpiperazines, the piperazine sub-structure occurs in many other pharmaceutical agents representing a wide range of pharmacological effects (e.g. diethylcarbamazine – an

(6) This report follows the format of Technical Annexes A–D as set out in 'Guidelines for the risk assessment of new synthetic drugs', EMCDDA, 1999. The information included reflects the situation as of May 2007.

antifilarial; vanoxerine — a dopamine reuptake inhibitor). But here, as elsewhere, the piperazine unit per se has no unique properties; it is best seen as a structural framework bearing nitrogen atoms, which, as in many other nitrogen-containing psychoactive substances, have an affinity for neuroreceptors. Substituted piperazines are unique chemical compounds; their structure is based on the piperazine moiety, but they do not 'contain' piperazine (King and Nutt, 2007).

Despite claims by some suppliers of tablets and capsules that they are herbal products, piperazine and its derivatives are synthetic substances that do not occur naturally. The suggestion that BZP and other piperazine derivatives are extracted from the pepper plant may arise from confusion with the unrelated substance piperine, a constituent of *Piper nigrum*.

Historical background to BZP

BZP was synthesised in the early 1940s by the Burroughs Wellcome Company (Buck and Balzty, 1947). It is often stated that BZP was originally developed as a potential anthelmintic 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 (?). The similarity of BZP to amphetamine was noted in early pharmacological studies (Bye et al., 1973; Campbell et al., 1973). One of the authors of that work was able to confirm that BZP was developed by Burroughs Wellcome as a potential antidepressant drug (Peck, 2007); its ability to reverse the effects of reserpine in rats had been noted some years earlier. Furthermore, there had been no commercial motivation to develop improved anthelmintic drugs since piperazine was, and still is, a successful treatment for intestinal worm infestations.

One of the first references to the use of BZP for 'recreational' purposes appeared in 1991, in the book 'Pihkal' (Shulgin and Shulgin, 1991). It was noted that BZP was 'active in the 20 to 100 milligram range, but which has an acceptability similar to amphetamine'. The possibility of ring-substituted derivatives of BZP was also briefly mentioned. Shortly thereafter, the Drug Enforcement Administration (DEA) reported misuse of BZP in California. According to the DEA, its popularity

(?) Burroughs Wellcome is now part of GlaxoSmithKline. Following enquiries, it appeared that there was no material in the company archives detailing investigations of BZP.

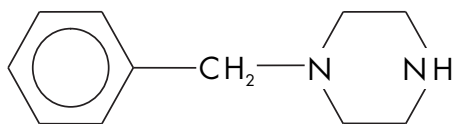
increased after 2000 as shown by the 'increasing encounters of this substance by law enforcement officials' (DEA, 2004).

In 1999, the Clandestine Laboratory Investigating Chemists Association produced the first collection of analytical data on BZP and related piperazine derivatives (Aunan and Ely, 1999). Also in 1999, Sweden made the first report of the misuse of BZP in Europe. However, BZP did not become more widespread as a recreational drug in the rest of Europe until the second half of 2004. Without doubt, BZP has been most prevalent in New Zealand, where some proponents have regarded it as a harm-minimisation measure, namely an alternative to methamphetamine. It is for this reason that much of the epidemiological and pharmacotoxicological data on BZP originate in that country. However, references to some of the research from New Zealand cited in Chapters 3 and 4 should be treated with caution, since that research may not translate to Europe. It should be recognised that there are considerable differences from Europe in other areas of drug use, partly caused by the geographical separation of New Zealand from the world's major drug-producing regions (Sheridan et al., 2007). The use of BZP as a 'legal high' has been described in recent articles in the British newspapers and popular press (McCandless, 2005; May, 2006; Vince, 2006).

Chemical description

The structure of 1-benzylpiperazine is shown in Figure 2. Other chemical names include 1-benzyl-1,4-diazacyclohexane, N-benzylpiperazine and, less precisely, benzylpiperazine or just BZP; it has no stereoisomers. BZP is normally produced as the dihydrochloride salt. 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). 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 phencyclidine and with 1-phenylethylamine and its derivatives (King et al., 1996).

Figure 2. Chemical structure of 1-benzylpiperazine (C₁₁H₁₆N₂)



The molecular weight of the base is 176.26 Daltons; the dihydrochloride is 249.19 Daltons. The Chemical Abstracts Service registry numbers of BZP are: 2759-28-6 (base) and 5321-63-1 (dihydrochloride).

BZP was widely available from retail chemical suppliers (e.g. Sigma Aldrich product reference 13815-25G-F), and there seems to be no need for illicit production. However, some suppliers have now withdrawn BZP from sale. It can be synthesised (Craig and Young, 1973) by reacting piperazine monohydrochloride with benzyl chloride. The latter precursor is readily available, and piperazine mono-hydrochloride is easily produced from the commercially-available dihydrochloride, phosphate or citrate salts. It is known that 1,4-dibenzylpiperazine (DBZP) can be formed as a side-product in this reaction.

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) and Button et al. (2007). Most of these rely either on GCMS or liquid chromatography coupled with mass spectrometry.

Legitimate use of BZP

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 antidepressant 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 (8) as a 'worming agent', but this is misleading since it has never been licensed as an anthelmintic drug. 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 in the EU.

Pharmaceutical form

BZP is usually found in illicit dosage forms, either as tablets or capsules, but loose powders also occur, some of which could have been sourced from legitimate chemical suppliers. Solutions of BZP were encountered less frequently. There are no licensed medicinal products containing BZP.

Routes of administration and dosage

Consumption of BZP is mainly by ingestion. In the New Zealand 'National household survey of legal party pill use' (Wilkins et al., 2006; Wilkins et al., 2007, see Studies on street users, below), 98.8 % of respondents ingested BZP/TFMPP. Although powders were commonly seen, only one individual (out of 2 010) claimed to have injected, two had snorted (insufflated), but none admitted to smoking the drug(s). In a survey of over 90 BZP-containing products available in New Zealand, the typical dose per unit was 50 to 200 mg (Sheridan, 2007). This correlates with dosages used in published trials (Bye et al., 1973 and Campbell et al., 1973).

(8) BBC News 27 April 2007, <http://news.bbc.co.uk/1/hi/health/6598309.stm> (accessed on 16 May 2007).

Pharmacology and toxicology in animals

Pre-clinical safety data

There are no published data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of BZP.

Pharmacodynamics

Neuropharmacology and *in vitro* tests

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 α_2 -adrenoreceptor antagonist, thereby inhibiting the pre-synaptic negative feedback mechanism (yohimbine-like and tyramine-like effect) (Magyar et al., 1986; and Magyar, 1987). However, an *in vitro* study using cortical slices of rat brain showed no presynaptic α_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 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-HT₂ receptors and both inhibition of 5-HT uptake and 5-HT₁ 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 (^3H)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, 2005). This was noted to be reminiscent of methamphetamine. TFMPP was found to be a selective releaser of 5-HT and led to 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 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, 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

No specific effects were noted in animal studies.

Behavioural studies

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). 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 (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 + TFMP 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).

Pharmacokinetics in animals

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, which compared to the ED_{50} of amphetamine (0.2 mg/kg) for the procedure used (Fantegrossi et al., 2005).

BZP appears to be metabolised by cytochrome P450 (possibly involving the CYP2D6 isoenzyme) 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 3-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 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 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 four hours which increased to 22.7:1 in 48 hours. No information was available on the toxicity of BZP metabolites.

Human pharmacology

Laboratory studies in volunteers

Effects on cognition and behaviour

In a study of former amphetamine addicts, 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 drugs. 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 checklist 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 a ten-fold higher effective potency.

Physiological effects

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.

Pharmacokinetics in humans

No human pharmacokinetic data are available for BZP: in particular, absorption, distribution, AUC, C_{max} , T_{max} and half-life. In humans, BZP is postulated to follow the same metabolic fate as in rats. This 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). Unlike animal studies, elimination data in humans are not available.

Clinical experience

Studies on street users

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 drugs (in particular MDMA and other serotonergic/dopaminergic compounds), but toxic effects with BZP alone have also 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 drug abusers, inmates, drug treatment patients, drivers and a fatality. In the vast majority of instances, other common drugs 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 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 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 have a history of seizures. 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 two tablets. Three cases of severe toxicity are mentioned below.

In the New Zealand household survey (Wilkins et al., 2006; Wilkins et al., 2007), 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 100 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 drugs of abuse.

(i) November 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.

(?) http://www.erowid.org/experiences/subs/exp_Piperazines_BZP.shtml and http://leda.lycaem.org/?Table=Trips&Ref_ID=415 (both accessed on 16 May 2007).

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) November 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. Coordination 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 ongoing feeling of anxiety and uneasiness.

(iii) February 2001 (USA?) — Sensory enhancement for the first two 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 four 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 three hours but not baseline after four 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.

In April 2007, tablets collected by the Sintes network in France were sent for analysis. The user had complained about a hangover disproportionate with the consumption of what he thought was MDMA. On the following day, he felt anxiety on waking, headache, general aching and depression. For two days, he suffered from slight nausea. He admitted to having taken two different tablets and five glasses of beer. Three other people consumed the same tablets and felt the same effects. It was found that one tablet contained MDMA and the other, BZP.

In New Zealand, a survey of telephone calls to the 'Drug Helpline' showed that, in 2004/2005, 81 (0.6 %) related to 'legal dance party pills' ⁽¹⁰⁾. By contrast, methamphetamine resulted in 1 489 calls (10.9 %).

Interactions with other drugs and medicines

Based on the pharmacology of BZP, there would be an expected interaction with other drugs 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 medications 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 ⁽¹¹⁾ indicate polydrug use is common as an intended adjunct to BZP use and many mention the additional use of these drugs 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 increased harm if the drugs 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

⁽¹⁰⁾ Cited in 'Legal party pills in New Zealand', background briefing note for Members of Parliament, 2 April 2007: <http://www.parliament.nz/NR/rdonlyres/BA1B0C14-698D-4ADF-A633-6687380FB255/53103/0702LegalPartyPills3.pdf> (accessed on 16 May 2007).

⁽¹¹⁾ http://www.erowid.org/experiences/subs/exp_Piperazines_BZP.shtml and http://leda.lycaeum.org/?Table=Trips&Ref_ID=415 (both accessed on 16 May 2007).

number of BZP tablets, reportedly due to a slow onset of action following oral use.

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, BZP is not always included in routine or targeted toxicological analysis, or may be detected but not identified as being BZP (Elliott et al., 2006, 2007).

Non-fatal cases

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

Patient 1: (16-year-old female, four 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, two pills with alcohol and two pills following morning) had a tonic seizure three 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, seven patients (18–23 years old) 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, five of the patients exhibited dilated pupils, anxiety, agitation and tachycardia. After eight hours of observation and

treatment with benzodiazepines, there was no evidence of continued toxicity. Serum samples were analysed in four 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, afebrile (temperature 35.9 °C) and had dilated pupils and a GCS of 15/15. She was discharged after 12 hours (Wood et al., 2007).

Between June–December 2006, BZP was detected in five patients elsewhere in the UK, with TFMP also detected in four of the cases (Elliott et al., 2006, 2007). All cases were confirmed by toxicological analysis as summarised below. No blood samples were available.

Case 1: May 2006 — 14-year-old male; urine BZP = 83.21 mg/L

Case 2: June 2006 — 32-year-old male; urine BZP = 35.75 mg/L, 3-TFMP = 0.40 mg/L

Case 3: October 2006 — 15-year-old female; urine BZP = 8.33 mg/L, 3-TFMP = 0.48 mg/L

Case 4: December 2006 — 26-year-old male; urine BZP ~ 39.87 mg/L, 3-TFMP ~ 12.13 mg/L. MDMA and methadone also present.

Case 5: December 2006 — 24-year-old male; urine BZP ~ 20.86 mg/L, 3-TFMP ~ 1.53 mg/L. MDMA, cocaine and quinine also present.

In Case 4, a 26-year-old male presented at an accident and emergency department 12 hours after having taken six blue 'legal high' tablets. Symptoms included chest pains, visual hallucinations, dizziness, drowsiness and dilated pupils (Elliott and George, 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.

Fatal cases

There have been very few instances of fatalities involving BZP. Three cases have been formally published (Wikström et al., 2004; Balmelli et al., 2001); Elliott (2006, 2008) has reported on three further cases, none of which involved BZP alone, and BZP was not the immediate cause of death.

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 seven 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 GCS of six. 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 the three fatal UK cases are set out below:

Case 1: (August 2006) — A 26-year-old male driver was involved in a fatal road traffic accident. Subsequent information indicated he may have used 'Wicked high' pills. Comprehensive toxicological analysis of post-mortem blood and urine samples found a urinary BZP of 15.73 mg/L, TFMPP (1.04 mg/L), cannabinoids, cocaine, ephedrine, 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: (August 2006) — A 32-year-old male was the driver of a 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, cannabinoids, 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 drugs present. Note: The atracurium and possibly cyclizine and diazepam were present as part of medical treatment. Diltiazem is sometimes found as an adulterant in illicit cocaine (Elliott, 2006).

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 drunk 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).

In all three cases, due to the toxicologically significant presence of other drugs and/or alcohol, it was 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. Furthermore, in New Zealand, it has been suggested by the Candor Trust — a road safety group ⁽¹²⁾ — that BZP appears to be a 'relatively low risk in real traffic situations'.

Dependence potential in humans

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 former addicts, 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'. Although some anecdotal reports from users on the Internet mention addiction and dependence, there are no clinical studies to

⁽¹²⁾ <http://www.candor.org.nz/> (accessed on 16 May 2007).

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.

Clinical safety

There are no specific studies regarding the clinical safety of BZP. However, it is believed that the potential antidepressant drug, piberaline, was not pursued, largely based on the results of studies involving BZP as its active metabolite.

Evidence of psychological risks

The only published human studies relating to psychological effects are those by Campbell et al. (1973) and Bye et al. (1973). These are described under 'Human pharmacology' (above), and 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.

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; Wilkins et al., 2007). However, none of the participants were confirmed BZP users.

Additional self-reports from users on the Internet ⁽¹³⁾ 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 that BZP made users much more sociable and enthusiastic. One user stated it allowed mental tasks to be performed for many hours without becoming fatigued. Conversely, another user stated that their coordination and intellectual

⁽¹³⁾ http://www.erowid.org/experiences/subs/exp_Piperazines_BZP.shtml and http://leda.lycaem.org/?Table=Trips&Ref_ID=415 (both accessed on 16 May 2007).

ability had been negatively affected. Others reported an ongoing 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 basis of these reports, it is difficult to make any definitive conclusions.

Chapter 4

Criminological and sociological evidence and public health risks

Criminological and sociological evidence

Although BZP is not a controlled substance in most EU Member States, it is inevitable that it would be seized by police and customs authorities, because BZP tablets and capsules resemble those of ecstasy and they usually bear typical logos. Since early 2007, BZP has been reported in 14 Member States ⁽¹⁴⁾ (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Malta, Netherlands, Portugal, Spain, Sweden and the United Kingdom) and Norway. Most were police/customs seizures, but some were 'collected samples' and some were detections in body fluids. In each Member State, most of the seizures occurred in just a small number of cases and many of these were of small amounts. The 'collected samples' were obtained either through tablet analysis schemes (the Netherlands, Austria) or by ad hoc test purchases (UK).

The two countries with both the largest number of seizures and the largest quantities of BZP seized, were Sweden and the United Kingdom. Since 2000, Sweden has reported 118 police seizures of BZP, many of which were in the south of the country. Almost half of the cases consisted of white, beige or yellow powders; the remainder were capsules in a variety of colours and, since 2003, tablets in various colours. Several seizures of powders were made by Swedish customs over the past five years, the largest being 23 kg together with parts of a tableting machine. By far the largest single seizure of BZP dosage units in Europe occurred in London in July 2006 when 64 900 tablets — together with firearms — were recovered from a vehicle. Two seizures involving a total of 5 379 tablets were made in Scotland in late 2006. The 'Mitsubishi' and 'Smiley face' design were common logos on these tablets.

There has been no direct evidence that BZP has been synthesised in Europe, although it is possible that tableting operations may exist. A small-scale

⁽¹⁴⁾ The Risk assessment report (Chapter 1) mentions that since early 2007, BZP has been reported in 13 Member States and not in 14. This difference is due to unavoidable delays in reporting.

'laboratory' was discovered in Germany in 2005 where both solids and liquids containing BZP were recovered.

There have been no reports of violence or money laundering in connection with wholesale production and distribution of BZP. Furthermore, there is no specific evidence of negative social consequences or linking the use of BZP to disorderly conduct, acquisitive crime or violence.

To address social consequences for users is to infer cause-effect relationships, which are not justified by the data on BZP. According to Sheridan (2007), even in New Zealand, where use of BZP is more common, such information is lacking. A conservative interpretation of this absence of evidence might indicate that BZP leads to very limited social harms.

Public health risks

A note of caution is required when interpreting the epidemiological data, whether it is from New Zealand or Europe, because, as noted above, many BZP-containing tablets and capsules also contain TFMPP. In the New Zealand research, they are often described as 'legal party pills'. In this situation, it is not clear which factors are solely due to BZP, which are solely due to TFMPP and which are due to the mixture. In this report, 'BZP' is used where the original literature may have used the term 'legal party pills'.

Availability and quality of product on the market

Availability at consumer level

BZP was first notified via the EMCDDA–Europol EWS in 1999, but the emergence of piperazine derivatives as recreational drugs with potential for rapid spread in Europe lay relatively latent until the second half of 2004, when various mCPP tablets appeared in the majority of the Member States, often designed to look like 'ecstasy' and almost always sold/bought as the popular drug ecstasy (Europol–EMCDDA, 2006). At approximately the same time, BZP-containing products started to be aggressively marketed in some EU Member States (for example, in

printed media and in various designated shops in the UK and Ireland) and on the Internet as a legal alternative to ecstasy. They were often specified as 'piperazine products' but erroneously or intentionally misrepresented as 'natural' or 'herbal'.

BZP is largely sold as tablets and capsules, often via Internet sites, some of which appear to be based in the European Union, in particular in the UK (¹⁵). Otherwise, in some Member States BZP can be purchased in 'smart shops' and 'legal high' stalls at festivals. Specific names for BZP-containing products include 'Jax', 'A2', 'pep twisted', 'pep love' and many others; generic terms for BZP-containing tablets and capsules include 'legal XTC', 'pep pills', 'social tonics' and 'party pills'. It is believed that many of these products originated in New Zealand, where a large market has developed for this substance. Many users will therefore have a clear idea that they are purchasing a distinct substance — BZP. On the illegal drugs market in the European Union, BZP may also be sold/bought as the popular drug ecstasy. Given this fact, the development of a parallel 'private', 'semi-public' or 'street' market could not be excluded.

Some of the UK Internet sites have now suspended sales following an investigation by the Medicines and Healthcare Products Regulatory Agency (¹⁶) into their legality under the Medicines Act (1968). However, it appears that these products can still be sourced directly from New Zealand (¹⁷). Beyond dosage units, it is likely that some pure material can still be obtained directly from chemical suppliers. Nevertheless, in late 2006, BZP was withdrawn by chemical suppliers such as Thermo Fischer (UK) and Acros (Belgium). Reportedly, Thermo Fischer had seen an increase in enquiries about BZP availability prior to its withdrawal from their catalogue (personal communication).

In its 'Final Rule' (DEA, 2004) on the placement of BZP into Schedule I of the US Controlled Substances Act, the DEA stated that 'BZP has increasingly been found in similar venues as the popular club drug MDMA'. BZP, often in combination with TFMPP, was sold as MDMA and promoted as an alternative to MDMA.

In New Zealand, products containing BZP (either alone or in combination with TFMPP) have often been marketed as 'herbal' and 'safe', and sold without

(¹⁵) For example, see: <http://www.spiritualhigh.co.uk>, <http://www.everyonedoesit.co.uk>, <http://www.pep-pills.co.uk/>, <http://www.redeyefrog.co.uk/>, <http://www.youknowit.com/>, <http://www.legal-highs-shop.co.uk/> and <http://www.wellcoolstuff.com/> (all accessed on 16 May 2007).

(¹⁶) <http://www.mhra.gov.uk/> (accessed on 23 May 2007).

(¹⁷) For example, see: <http://www.pep-pills.co.nz/> (accessed on 16 May 2007).

regulation since 2000. Since mid-2004, they have become widely available and are commonly used by young people (Gee et al., 2005). Estimates suggest that 50 000 four-tablet packs of party pills are sold in New Zealand every month (Sheridan et al., 2007), and that annual sales are worth around EUR 20 million. The individual characteristics of different products appear to be achieved largely by varying the ratio and quantities of BZP and TFMPP, to achieve the desired level of stimulant versus empathic and hallucinogenic effects.

Average dose and degree of variability

Although the (qualitative) content of BZP party pills was more or less correctly marked on containers, this was not always the case with the quantity of drug present in each tablet. In a study by Kenyon et al. (2007), various BZP tablets were purchased from three different Internet suppliers. Of 20 tablets and capsules, the mean BZP content was 65 mg (range 28 to 133 mg). Most also contained TFMPP, the mean content of which was 22 mg (range 4 to 72 mg). For comparison, the content on the packaging was claimed to be 105 to 200 mg (BZP) and 50 to 75 mg (TFMPP). Sheridan et al. (2007) reported that some products in New Zealand contained 100 mg BZP, but in other cases only the total amount of piperazine-derivatives (e.g. BZP + TFMPP) was noted on the packaging.

Purity levels and presence of adulterants

It is quite common for BZP products to be described, either erroneously or intentionally, as 'natural' or 'herbal'. In some countries, BZP was originally marketed as a 'nutritional supplement'. Apart from TFMPP, BZP tablets were advertised as also containing herbal ingredients such as extract of black pepper (piperine). Little information was available on the presence — in BZP tablets and capsules — of other pharmacologically inactive adulterants (e.g. sugars, inorganic fillers), but since many dosage units weighed approximately 300 mg, it may be assumed that more than half of the tablet weight comprised other active or inactive substances.

Other active ingredients

BZP was often mixed with other piperazine derivatives. The most common was TFMP (1-(3-trifluoromethyl-phenyl)piperazine), but MeOPP (1-(4-methoxy-phenyl)-piperazine), mCPP (1-(3-chlorophenyl)-piperazine), MPP (4-methylphenylpiperazine), 1-benzyl-4-methylpiperazine and DBZP (1,4-dibenzylpiperazine) also occurred although, as discussed above, DBZP may have been a synthetic by-product. A number of other active substances were found mixed with BZP; they included tripeleminamine, cocaine, caffeine, 2-phenylethylamine, ketamine, sildenafil, phenazone, nicotineamide, chavicine (a constituent of black pepper) and MDMA. In Sweden, almost all BZP tablets also contained caffeine. BZP sometimes occurred as a minor ingredient in MDMA tablets. In New Zealand (Sheridan et al., 2007), l-tyrosine is added to some BZP tablets or sold separately in so-called 'recovery pills'. This amino acid is a metabolic precursor to dopamine, and may, theoretically, help to alleviate dopamine depletion caused by BZP. Other amino acids may also be added as well as vitamins and 'electrolyte blends' such as sodium, potassium, magnesium and calcium salts. Whether any of these additives have any beneficial effect is questionable.

Typical prices and range

Tablets and capsules purchased from UK websites (see 'Availability at consumer level', above) cost around EUR 4 per unit.

Knowledge, perceptions and availability of information

Availability of scientific information on the product

Compared to many of the 'new synthetic drugs' encountered in Europe in the last 10 years, there is a large amount of scientific literature available on BZP. However, there have been few direct investigations of its pharmacology, and almost nothing has been published on the social consequences of BZP use. Apart from a number of anecdotal reports from users published on Internet sites⁽¹⁸⁾, most studies of the effects of BZP have been made by research groups in New Zealand.

⁽¹⁸⁾ For example, see: http://www.erowid.org/experiences/subs/exp_Piperazines_BZP.shtml (accessed on 16 May 2007).

As with any drug use, lack of scientific and objective information may contribute towards increased risks. Firstly, inaccurate media coverage may promote diffusion by encouraging young people to try BZP. And secondly, official dissemination of inaccurate information may be counterproductive, as it can undermine credibility.

Level of knowledge of BZP, effects and perceptions among consumers

The appearance of ecstasy logos on BZP tablets suggests that this substance is partly sold and purchased as ecstasy, but many users, particularly those purchasing from Internet sites, will have a clear idea that they are ingesting a specific substance that is different to ecstasy. The major positive attributes of BZP in New Zealand were described by Wilkins et al. (2006, 2007) as being: energy, euphoria, legality, cost, ease of purchase, enhanced sociability and safer than alternatives. The perceived safety of BZP seems to be fostered by the fact that the products are often sold by designated retailers or in specialised shops rather than on the street, and furthermore, the content is visibly stated.

Although not as highly regarded by users as, for example, ecstasy, the marked psychoactive effects of BZP (stimulant or ecstasy-like when combined with TFMPP) may contribute to its popularity. For users who are aware of the fact that they are consuming BZP, i.e. those who purchased it as such, it seems that this drug may have a certain appeal. However, this specific demand or market for BZP-containing products may be due to their legal status and accessibility.

All these factors may have contributed to the establishment of BZP as a recreational drug of choice in its own right. Together with mCPP, BZP seems to be one of the most popular piperazine derivatives in Europe. A French outreach investigator reported a particular interest for this substance in the context of a festival in the south of France, where the users reported that they wanted to distinguish themselves from traditional synthetic drug users. Apart from published prices on Internet sites, little or no information is available on the price of BZP on the illegal drugs market in the Member States.

In New Zealand, BZP-containing products have been promoted as a 'harm minimisation solution' and a safer alternative to methamphetamine, yet there is little evidence to support these claims. Wilkins et al. (2006, 2007) looked for evidence of a gateway effect by examining a group of people who had used both BZP and illegal drugs in the previous year. However, in the absence of control groups (i.e.

never used drugs, only used BZP, only used illegal drugs), it is difficult to determine from the data presented whether BZP led to a greater or lower use of illegal drugs.

Amongst those who do not use BZP, there is a widespread belief, often promoted by the media, that BZP is a 'worming medicine' used in veterinary practice.

Prevalence and patterns of use

In New Zealand, the 2006 'National household survey of legal party pill use' provides some national population statistics on the prevalence and patterns of BZP consumption (Wilkins et al., 2006; Wilkins et al., 2007). The results for 2 010 respondents are shown in Table 1.

Table 1. Prevalence of use of BZP (Wilkins et al., 2006)

Age group	Ever used (%)	Used in last year (%)	Used in last month (%)
13–14 years	3.0	3.0	Not available
15–17 years	16.3	16.3	5.8
18–19 years	40.7	33.9	13.1
20–24 years	48.8	38.0	10.5
All	20.3	15.3	4.6

One in five (20.3 %; range 18.4–22.3 %) of the sample had ever tried legal party pills, and one in seven (15.3 %; range 13.6–17.1 %) had used legal party pills in the preceding 12 months.

Levels of last year use of legal party pills were highest among the 18–24 year-old age group with 33.9 % (range 25.3–43.6 %) of 18–19-year olds and 38.0 % (range 31.3–45.2 %) of 20–24-year olds having used legal party pills in the preceding year.

Males were more likely than females to have used legal party pills in the previous year in a number of age groups, including among 13–14-year olds (4.4 % vs. 0 %), 20–24-year olds (48.5 % vs. 27.9 %, $p=0.0043$), 30–34-year olds (15.4 % vs. 6.6 %, $p=0.0179$), 35–39-year olds (10.7 % vs. 2.2 %, $p=0.0032$) and 40–45-year olds (7.6 % vs. 2.5 %, $p=0.0252$).

Wilkins et al. (2006, 2007) found that almost half of those who had taken BZP in the last 12 months, had taken it once or twice only. About 6 % of the sample had used BZP weekly, or more often, in the past year. The mean number of BZP dosage units consumed was 2.6 (Wilkins et al., 2006; Wilkins et al., 2007). Four out of ten of the survey respondents claimed to have used four or more units on a single occasion, one in five had used six or more and one in nine had used eight or more on a single occasion.

In a survey conducted by Nicholson (2006), persons of all ages presenting to a New Zealand hospital emergency department were asked to complete a questionnaire. Of 1 043 responses, 12 % admitted to having ever used BZP.

Sheridan and Butler (2006) reported that BZP products are consumed amongst friends in social gatherings, but there have been no specific studies of the characteristics of BZP users in Europe. However, it appears that users of BZP are not a homogeneous group. It is likely that they include individuals who would by choice not use illegal drugs, but also users of ecstasy and amphetamine/methamphetamine who are willing to use other illicit drugs.

Other drugs used in combination with BZP

In the New Zealand 2006 'National household survey of legal party pill use' (Wilkins et al, 2006; Wilkins et al., 2007), nearly nine out of ten said they used other substances with BZP. The most common substances were alcohol (91.1 %), tobacco (39.6 %), and cannabis (22.3 %). The group had a much higher use of other drugs than the general population. For example, around 15 % had used 'amphetamines' in the past year compared to only 3.7 % of the population in 2003. Sheridan (2007) noted that 60–70 % of those already using hallucinogens, cannabis or methamphetamine were also consuming BZP/TFMPP.

Risk behaviours associated with BZP use

Sheridan (2007) refers to a number of risky behaviours amongst those using BZP in New Zealand. These include concomitant consumption of alcohol and other psychoactive substances, driving whilst under the influence, going for long periods without sleep, and taking more than the 'advised dose'. There have been no studies on the effect of BZP on driving skills. An unpublished study mentioned by

Sheridan (2007) suggested that BZP improved driving performance, but the study had to be terminated because the participants suffered severe adverse effects.

Other health indicators

Gee et al. (2005) warned that consumption of BZP should be avoided by those with seizure disorders, coronary disease or those taking prescription sympathomimetics or anticholinergics.

Sheridan and Butler (2006) noted the following negative effects of 'party pill' use: loss of appetite, increased rate of smoking and after-effects (the 'comedown'), which included headaches, lethargy and nausea.

In her survey, Nicholson (2006) 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.

In so far as BZP is almost always ingested in the form of dosage units, there appear to be no particular risk factors arising from the circumstances of its use.

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Council decision

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on European Union, and in particular Articles 29, 31(1)(e) and 34 (2)(c) thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament ⁽¹⁹⁾,

Whereas:

- (1) The particular dangers inherent in the development of psychoactive substances require rapid action by the Member States.
- (2) When new psychoactive substances are not brought within the scope of criminal law in all Member States, problems may arise in cooperation between the judicial authorities and law enforcement agencies of Member States owing to the fact that the offence or offences in question are not punishable under the laws of both the requesting and the requested State.
- (3) The European Union Action Plan on Drugs 2000–04 provided for the Commission to organise an appropriate assessment of the Joint Action of 16 June 1997 concerning the information exchange, risk assessment and the control of new synthetic drugs ⁽²⁰⁾ (hereinafter ‘the Joint Action’) taking into account the external evaluation commissioned by the European Monitoring Centre on Drugs and Drug Addiction (hereinafter ‘the EMCDDA’) of the early warning system. The assessment showed that the Joint Action had fulfilled its expectations. Nevertheless, the outcome of the assessment made it clear that the Joint Action was in need of reinforcement and reorientation. In

⁽¹⁹⁾ Opinion delivered on 13 January 2004 (not yet published in the Official Journal).

⁽²⁰⁾ OJ L 167, 25.6.1997, p. 1.

particular, its main objective, the clarity of its procedures and definitions, the transparency of its operation, and the relevance of its scope had to be redefined. The Communication from the Commission to the European Parliament and the Council on the mid-term evaluation of the EU Action Plan on Drugs (2000–04) indicated that changes to the legislation would be introduced in order to enhance action against synthetic drugs. The mechanism as established by the Joint Action should therefore be adapted.

- (4) New psychoactive substances can be harmful to health.
- (5) The new psychoactive substances covered by this Decision may include medicinal products as defined in Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to veterinary medicinal products ⁽²¹⁾ and in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use ⁽²²⁾.
- (6) The information exchange under the early warning system, established under the Joint Action, has proved to be a valuable asset to the Member States.
- (7) Nothing in this Decision should prevent Member States from exchanging information, within the European Information Network on Drugs and Drug Addiction (hereinafter 'the Reitox network'), on emerging trends in new uses of existing psychoactive substances which may pose a potential risk to public health, as well as information on possible public health related measures, in accordance with the mandate and procedures of the EMCDDA.
- (8) No deterioration of either human or veterinary health care as a result of this Decision will be permitted. Substances of established and acknowledged medical value are therefore excluded from control measures based on this Decision. Suitable regulatory and public health related measures should be taken for substances of established and acknowledged medical value that are being misused.
- (9) In addition to what is provided for under the pharmacovigilance systems as defined in Directive 2001/82/EC and in Directive 2001/83/EC, the exchange of information on abused or misused psychoactive substances needs to be reinforced and appropriate cooperation with the European

⁽²¹⁾ OJ L 311, 28.11.2001, p. 1. Directive as last amended by Directive 2004/28/EC (OJ L 136, 30.4.2004, p. 58).

⁽²²⁾ OJ L 311, 28.11.2001, p. 67. Directive as last amended by Directive 2004/27/EC (OJ L 136, 30.4.2004, p. 34).

Medicines Agency (hereinafter 'EMA') ensured. The United Nations Commission on Narcotic Drugs (hereinafter 'CND') Resolution 46/7 'Measures to promote the exchange of information on new patterns of drug use and on psychoactive substances consumed', provides a useful framework for action by the Member States.

- (10) The introduction of deadlines into every phase of the procedure established by this Decision should guarantee that the instrument can react swiftly and enhances its ability to provide a quick-response mechanism.
- (11) The Scientific Committee of the EMCDDA has a central role in the assessment of the risks associated with a new psychoactive substance, it will for the purpose of this Decision be extended to include experts from the Commission, Europol and the EMA, and experts from scientific fields not represented, or not sufficiently represented, in the Scientific Committee of the EMCDDA.
- (12) The extended Scientific Committee that assesses the risks associated with new psychoactive substances should remain a concise technical body of experts, capable of assessing effectively all risks associated with a new psychoactive substance. Therefore the extended Scientific Committee should be kept to a manageable size.
- (13) Since the objectives of the proposed action, namely to bring about an exchange of information, a risk-assessment by a scientific committee and an EU-level procedure for bringing notified substances under control, cannot be sufficiently achieved by the Member States and can therefore, by reason of the effects of the envisaged action, be better achieved at European Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty. In accordance with the principle of proportionality as set out in that Article, this Decision does not go what is beyond what is necessary in order to achieve those objectives.
- (14) In conformity with Article 34(2)(c) of the Treaty, measures based upon this Decision can be taken by qualified majority as these measures are necessary to implement this Decision.
- (15) This Decision respects fundamental rights and observes the principles recognised by Article 6 of the Treaty and reflected in the Charter of Fundamental Rights of the European Union,

HAS DECIDED AS FOLLOWS:

Article 1

Subject matter

This Decision establishes a mechanism for a rapid exchange of information on new psychoactive substances. It takes note of information on suspected adverse reactions to be reported under the pharmacovigilance system as established by Title IX of Directive 2001/83/EC.

This Decision also provides for an assessment of the risks associated with these new psychoactive substances in order to permit the measures applicable in the Member States for control of narcotic and psychotropic substances to be applied also to new psychoactive substances.

Article 2

Scope

This Decision applies to substances not currently listed in any of the schedules to:

- (a) the 1961 United Nations Single Convention on Narcotic Drugs, that may pose a comparable threat to public health as the substances listed in Schedule I or II or IV thereof, and
- (b) the 1971 United Nations Convention on Psychotropic Substances, that may pose a comparable threat to public health as the substances listed in Schedule I or II or III or IV thereof.

This Decision relates to end-products, as distinct from precursors in respect of which Council Regulation (EEC) No 3677/90 of 13 December 1990 laying down measures to be taken to discourage the diversion of certain substances to the illicit manufacture of narcotic drugs and psychotropic substances ⁽²³⁾, and Regulation (EC) No 273/2004 of the European Parliament and of the Council of 11 February 2004 on drug precursors ⁽²⁴⁾ provide for a Community regime.

⁽²³⁾ OJ L 357, 20.12.1990, p. 1. Regulation as last amended by Commission Regulation (EC) No 1232/2002 (OJ L 180, 10.7.2002, p. 5).

⁽²⁴⁾ OJ L 47, 18.2.2004, p. 1.

Article 3

Definitions

For the purpose of this Decision the following definitions shall apply:

- (a) 'new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation;
- (b) 'new narcotic drug' means a substance in pure form or in a preparation, that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV;
- (c) 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV;
- (d) 'marketing authorisation' means a permission to place a medicinal product on the market, granted by the competent authority of a Member State, as required by Title III of Directive 2001/83/EC (in the case of medicinal products for human use) or Title III of Directive 2001/82/EC (in the case of veterinary medicinal products) or a marketing authorisation granted by the European Commission under Article 3 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency ⁽²⁵⁾;
- (e) 'United Nations system' means the World Health Organisation (WHO), the Commission on Narcotic Drugs (CND) and/or the Economic and Social Committee acting in accordance with their respective responsibilities as described in Article 3 of the 1961 United Nations Single Convention on Narcotic Drugs or in Article 2 of the 1971 United Nations Convention on Psychotropic Substances;
- (f) 'preparation' means a mixture containing a new psychoactive substance;
- (g) 'Reporting Form' means a structured form for notification of a new psychoactive substance and/or of a preparation containing a new psychoactive

⁽²⁵⁾ OJ L 136, 30.4.2004, p. 1.

substance agreed between the EMCDDA/Europol and their respective networks in the Member States' Reitox and the Europol national units.

Article 4

Exchange of information

- (1) Each Member State shall ensure that its Europol National Unit and its representative in the Reitox network provide information on the manufacture, traffic and use, including supplementary information on possible medical use, of new psychoactive substances and of preparations containing new psychoactive substances, to Europol and the EMCDDA, taking into account the respective mandates of these two bodies.

Europol and the EMCDDA shall collect the information received from Member States through a Reporting Form and communicate this information immediately to each other and to the Europol National Units and the representatives of the Reitox network of the Member States, the Commission, and to the EMEA.

- (2) Should Europol and the EMCDDA consider that the information provided by a Member State on a new psychoactive substance does not merit the communication of information as described in paragraph 1, they shall inform the notifying Member State immediately thereof. Europol and the EMCDDA shall justify their decision to the Council within six weeks.

Article 5

Joint Report

- (1) Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report (hereinafter the 'Joint Report'). The Joint Report shall be submitted to the Council, the EMEA and the Commission.

- (2) The Joint Report shall contain:
- (a) a chemical and physical description, including the name under which the new psychoactive substance is known, including, if available, the scientific name (International Non-proprietary Name);
 - (b) information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance;
 - (c) information on the involvement of organised crime in the manufacture or trafficking of the new psychoactive substance;
 - (d) a first indication of the risks associated with the new psychoactive substance, including the health and social risks, and the characteristics of users;
 - (e) information on whether or not the new substance is currently under assessment, or has been under assessment, by the UN system;
 - (f) the date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol;
 - (g) information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State;
 - (h) as far as possible, information will be made available on:
 - (i) the chemical precursors that are known to have been used for the manufacture of the substance,
 - (ii) the mode and scope of the established or expected use of the new substance,
 - (iii) any other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks.
- (3) The EMEA shall submit to Europol and the EMCDDA the following information on whether in the European Union or in any Member State:
- (a) the new psychoactive substance has obtained a marketing authorisation;
 - (b) the new psychoactive substance is the subject of an application for a marketing authorisation;

- (c) a marketing authorisation that had been granted in respect of the new psychoactive substance has been suspended.

Where this information relates to marketing authorisations granted by Member States, these Member States shall provide the EMEA with this information if so requested by it.

- (4) Member States shall provide the details referred to under paragraph 2 within six weeks from the date of notification on the Reporting Form as set out in Article 4(1).
- (5) The Joint Report shall be submitted no more than four weeks after the date of receipt of the information from Member States and the EMEA. The Report shall be submitted by Europol or the EMCDDA, as appropriate, in accordance with Article 5(1) and (2).

Article 6

Risk assessment

- (1) The Council, taking into account the advice of Europol and the EMCDDA, and acting by a majority of its members, may request that the risks, including the health and social risks, caused by the use of, the manufacture of, and traffic in, a new psychoactive substance, the involvement of organised crime and possible consequences of control measures, be assessed in accordance with the procedure set out in paragraphs 2 to 4, provided that at least a quarter of its members or the Commission have informed the Council in writing that they are in favour of such an assessment. The Member States or the Commission shall inform the Council thereof as soon as possible, but in any case within four weeks of receipt of the Joint Report. The General Secretariat of the Council shall notify this information to the EMCDDA without delay.
- (2) In order to carry out the assessment, the EMCDDA shall convene a special meeting under the auspices of its Scientific Committee. In addition, for the purpose of this meeting the Scientific Committee may be extended by a further five experts at most, to be designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel of experts proposed by Member States and

approved every three years by the Management Board of the EMCDDA. Such experts will be from scientific fields that are not represented, or not sufficiently represented, in the Scientific Committee, but whose contribution is necessary for the balanced and adequate assessment of the possible risks, including health and social risks. Furthermore, the Commission, Europol and the EMEA shall each be invited to send a maximum of two experts.

- (3) The risk assessment shall be carried out on the basis of information to be provided to the scientific Committee by the Member States, the EMCDDA, Europol, the EMEA, taking into account all factors which, according to the 1961 United Nations Single Convention on Narcotic Drugs or the 1971 United Nations Convention on Psychotropic Substances, would warrant the placing of a substance under international control.
- (4) On completion of the risk assessment, a report (hereinafter the 'Risk Assessment Report') shall be drawn up by the Scientific Committee. The Risk Assessment Report shall consist of an analysis of the scientific and law enforcement information available, and shall reflect all opinions held by the members of the Committee. The Risk Assessment Report shall be submitted to the Commission and Council by the chairperson of the Committee, on its behalf, within a period of twelve weeks from the date of the notification by the General Secretariat of the Council to the EMCDDA referred to in paragraph 1.

The Risk Assessment Report shall include:

- (a) the physical and chemical description of the new psychoactive substance and its mechanisms of action, including its medical value;
- (b) the health risks associated with the new psychoactive substance;
- (c) the social risks associated with the new psychoactive substance;
- (d) information on the level of involvement of organised crime and information on seizures and/or detections by the authorities, and the manufacture of the new psychoactive substance;
- (e) information on any assessment of the new psychoactive substance in the United Nations system;

- (f) where appropriate, a description of the control measures that are applicable to the new psychoactive substance in the Member States;
- (g) options for control and the possible consequences of the control measures, and
- (h) the chemical precursors that are used for the manufacture of the substance.

Article 7

Circumstances where no risk assessment is carried out

- (1) No risk assessment shall be carried out in the absence of a Europol/EMCDDA Joint Report. Nor shall a risk assessment be carried out where the new psychoactive substance concerned is at an advanced stage of assessment within the United Nations system, namely once the WHO expert committee on drug dependence has published its critical review together with a written recommendation, except where there is significant new information that is relevant in the framework of this Decision.
- (2) Where the new psychoactive substance has been assessed within the United Nations system, but it has been decided not to schedule the new psychoactive substance under the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, a risk assessment shall be carried out only if there is significant new information that is relevant in the framework of this Decision.
- (3) No risk assessment shall be carried out on a new psychoactive substance if:
 - (a) the new psychoactive substance is used to manufacture a medicinal product which has been granted a marketing authorisation; or,
 - (b) the new psychoactive substance is used to manufacture a medicinal product for which an application has been made for a marketing authorisation or,
 - (c) the new psychoactive substance is used to manufacture a medicinal product for which a marketing authorisation has been suspended by a competent authority.

Where the new psychoactive substance falls into one of the categories listed under the first subparagraph, the Commission, on the basis of data collected by EMCDDA and Europol, shall assess with the EMEA the need for further action, in

close cooperation with the EMCDDA and in accordance with the mandate and procedures of the EMEA.

The Commission shall report to the Council on the outcome.

Article 8

Procedure for bringing specific new psychoactive substances under control

- (1) Within six weeks from the date on which it received the Risk Assessment Report, the Commission shall present to the Council an initiative to have the new psychoactive substance subjected to control measures. If the Commission deems it is not necessary to present an initiative on submitting the new psychoactive substance to control measures, within six weeks from the date on which it received the Risk Assessment Report, the Commission shall present a report to the Council explaining its views.
- (2) Should the Commission deem it not necessary to present an initiative on submitting the new psychoactive substance to control measures, such an initiative may be presented to the Council by one or more Member States, preferably not later than six weeks from the date on which the Commission presented its report to the Council.
- (3) The Council shall decide, by qualified majority and acting on an initiative presented pursuant to paragraph 1 or 2, on the basis of Article 34(2) (c) of the Treaty, whether to submit the new psychoactive substance to control measures.

Article 9

Control measures taken by Member States

- (1) If the Council decides to submit a new psychoactive substance to control measures, Member States shall endeavour to take, as soon as possible, but no later than one year from the date of that decision, the necessary measures in accordance with their national law to submit:
 - (a) the new psychotropic drug to control measures and criminal penalties as provided under their legislation by virtue of their obligations under the 1971 United Nations Convention on Psychotropic Substances;

- (b) the new narcotic drug to control measures and criminal penalties as provided under their legislation by virtue of their obligations under the 1961 United Nations Single Convention on Narcotic Drugs.
- (3) Member States shall report the measures taken to both the Council and the Commission as soon as possible after the relevant decision has been taken. Thereafter this information shall be communicated to the EMCDDA, Europol, the EMEA, and the European Parliament.
- (4) Nothing in this Decision shall prevent a Member State from maintaining or introducing on its territory any national control measure it deems appropriate once a new psychoactive substance has been identified by a Member State.

Article 10

Annual report

The EMCDDA and Europol shall report annually to the European Parliament, the Council and the Commission on the implementation of this Decision. The report will take into account all aspects required for an assessment of the efficacy and achievements of the system created by this Decision. The Report shall, in particular, include experience relating to coordination between the system set out in this Decision and the pharmacovigilance system.

Article 11

Pharmacovigilance system

Member States and the EMEA shall ensure an appropriate exchange of information between the mechanism set up by means of this Decision and the pharmacovigilance systems as defined and established under Title VII of Directive 2001/82/EC and Title IX of Directive 2001/83/EC.

Article 12

Repeal

The Joint Action on New Synthetic Drugs of 16 June 1997 is hereby repealed. Decisions taken by the Council based on Article 5 of that Joint Action shall continue to be legally valid.

Article 13

Publication and taking effect

This Decision shall take effect on the day following that of its publication in the *Official Journal of the European Union*.

Done at Brussels, 10 May 2005.

For the Council
The President
J. Krecké

European Monitoring Centre for Drugs and Drug Addiction

**Report on the risk assessment of BZP in the framework of the
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About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is one of the European Union's decentralised agencies. Established in 1993 and based in Lisbon, it is the central source of comprehensive information on drugs and drug addiction in Europe.

The EMCDDA collects, analyses and disseminates factual, objective, reliable and comparable information on drugs and drug addiction. In doing so, it provides its audiences with an evidence-based picture of the drug phenomenon at European level.

The Centre's publications are a prime source of information for a wide range of audiences including policymakers and their advisors, professionals and researchers working in the drugs field and, more broadly, the media and general public.

EMCDDA risk assessments are publications examining the health and social risks of individual synthetic drugs on the basis of research carried out by the agency and its partners.



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