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Risk Assessment Report

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

In accordance with Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances

1. Introduction

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances[1] (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[2] 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[3] 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 (EMEA) a Joint Report on the new psychoactive substance 1-benzylpiperazine (BZP) (6645/07 CORDROGUE 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.

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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.

3 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 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 twelve weeks from the date of the notification by the General Secretariat of the Council.

2. The 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 anthelminthic drug, e.g. in the treatment of intestinal round worm infestations. Piperazine itself has no psychoactive properties. However, BZP was never developed as a potential anthelminthic 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 1970's when it was found that BZP was a central nervous system (CNS) stimulant with similar properties to amphetamine. In the 1980's, BZP was used by the EGYT (now EGIS) pharmaceutical company in Hungary to manufacture the active substance piberaline (1-(phenylmethyl)-4-(2-pyridinylcarbonyl)-piperazine). This was marketed in Hungary as an anti-depressant under the proprietary name Trelibet®, which was later withdrawn. Piberaline metabolises to BZP, which may have been partly responsible for its activity.

3. The 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 requires nevertheless 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 4g of piperazine phosphate in a standard therapeutic dose: a quantity that is theoretically convertible into over 3g 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.

4. The 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 100mg. 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 iso-enzyme) 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[4].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.

5. The 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.

[4] 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 4 on the combined 5 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.

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 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.

6. 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, and 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.

As of May 2007, BZP had been reported in seizures in thirteen 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, 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 23kg together with parts of a tabletting 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 tabletting/encapsulating operations may exist.

7. Information on any assessment of BZP in the United Nations system

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

8. The control measures that are applicable to BZP

In twenty 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, as of 18 November 2004, BZP is 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 Third Schedule of the Medical and Kindred Professions Ordinance (Chapter 31). Substances controlled in the same list include MDMA, PMA, 2C-T-2. In Greece, as of 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, as of 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 6 years of imprisonment. Other substances under the same control include: mCPP, ketamine, *Ephedra* extracts and methylone.

In Spain, BZP is considered a substance which, 'when administered to human beings, modify 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 pharmaceutical inspectorate and customs, manufacturers, traders, importers or distributors working with this substance must notify annually their activities to Spanish Medicines Agency. Furthermore, authorities can exert enforcement actions on these companies, including suspension of activities.

9. Options for control and the possible consequences of the control measures

Under Article 9.1 of the 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 the 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.

10. Summary findings

10.1 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 TFMPP (1-(3-trifluoromethyl-phenyl)piperazine). On the illegal drugs market, BZP may also be sold/bought as the popular drug ecstasy.

10.2 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.

10.3 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.

10.4 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.

10.5 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.

10.6 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.

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

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

10.9 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.

11. 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 then an argument must 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