



EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION

**Report on the Risk Assessment of MBDB
in the Framework of the
Joint Action on New Synthetic Drugs**

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1. Introduction

1.1 Date of introduction of Joint Action, purpose and scope (Document I)

The Joint Action on new synthetic drugs was adopted by the European Council on 16 June 1997 in Amsterdam (O.J. no. L 167 of 25.06.1997).

The purpose of the Joint Action is the creation of a mechanism for rapid exchange of information on new synthetic drugs and the assessment of their risks in order to permit the application of the measures of control on psychotropic substances, applicable in the Member States, equally to new synthetic drugs (Article 1). Common action can be taken only on the basis of reliable information and the results of expert assessment of the risks caused by the use of and the trafficking in new synthetic drugs and the implications of submitting such drugs to control.

The scope of the Joint Action focuses on psycho-active substances (end-products, not precursors) with limited therapeutic value, which are not currently listed in any of the Schedules to the 1971 UN Convention on Psychotropic Substances and which pose potentially comparable public-health risks as the substances listed in Schedules I or II of this Convention (Article 2).

1.2 Notification of MBDB by the UK Presidency (Document II)

The implementation of the Joint Action on new synthetic drugs started formally in January 1998. The EMCDDA and Europol had already begun testing a common reporting form to collect and exchange information in the framework of the 'early-warning system' (Article 3).

On 27 February 1998, on behalf of all Member States, the United Kingdom Presidency of the European Union formally referred a new synthetic drug N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (or MBDB) to the EMCDDA for risk assessment under Article 4. On 4 March 1998, the Horizontal Drugs Group of the Council of the European Union requested all Member States to report any relevant information to Europol or the EMCDDA by means of Article 3.

1.3 Exchange of information on MBDB (Article 3)

In the context of Article 3, the EMCDDA and Europol collected and exchanged a first set of information about MBDB. This information was communicated to the Commission and to the European Agency for the Evaluation of Medicinal Products (EMA). On 15 May 1998, the EMCDDA and Europol submitted a joint progress report to the Chairman of the Horizontal Drugs Group of the Council and the Council Secretariat. The joint Report was presented by the EMCDDA and Europol at the Horizontal Drugs Group meeting of 20 May 1998 (Document III).

1.4 Implementation of the risk assessment of MBDB (Article 4)

The risk assessment focuses on the evaluation of the possible risks, including the health and social risks, caused by the use of, and traffic in, new synthetic drugs, and possible consequences of prohibition. The risk assessment on MBDB has been carried out on the basis of the information provided by the Member States, the Commission, the EMCDDA, Europol and the EMEA.

The risks of MBDB were assessed by the special meeting convened by the EMCDDA under the auspices of its Scientific Committee. This meeting was held at the EMCDDA in Lisbon on 9–10 November 1998, and chaired by Dr Desmond Corrigan, Chairperson of the Scientific Committee. The Committee designated Dr Salme Ahlström, Vice-Chairperson of the Scientific Committee, as the Rapporteur of the special meeting for risk assessment of MBDB.

According to Article 4, the participants in this special meeting are the following:

- Members of the Scientific Committee of the EMCDDA.
- Additional experts nominated by the Member States to participate in the special meeting for risk assessment of MBDB.
- Representatives of the Commission, Europol and the EMEA.

1.5 Report on the risk assessment of MBDB

Article 4.3 states: 'On completion of the risk assessment, a report will be drawn upon the findings. In the report all aspects shall be addressed. All opinions on these aspects shall be reflected in the report.'

According to Article 5, the report will be forwarded to the Council: 'The Council may, on the basis of an initiative to be presented within a month from the date on which the report of the results of the risk assessment pursuant to Article 4 (1) is established and acting in accordance with Article K.3 (2) (b) of the Treaty, adopt unanimously a decision defining the new synthetic drug or drugs which are to be made subject to necessary measures of control'.

1.6 Documentation considered

- Text of the Joint Action of 16 June 1997.
- Formal referral of MBDB to the EMCDDA.
- Joint EMCDDA–EDU Progress Report (20.05.98) – Chapter II: Preliminary information on MBDB collected and exchanged under Article 3 of the Joint Action.
- An Outline of Principles for Risk Assessment of New Synthetic Drugs (Guidelines) ST/SCO/9/98 (rev. 1).
- Technical Annexes A and B: The pharmacotoxicology and neuropsychology of MBDB, Report to the EMCDDA. Doc. NO. ST/SCO/10/98.
- Technical Annex D: Public health risks: epidemiological evidence, EMCDDA.
- Technical Annex C: Sociological/criminological evidence, EMCDDA.
- Europol contribution to the risk assessment on MBDB.
- Existing legal provisions: MBDB, Legal Situation in the EU Member States, EMCDDA background document.
- National Risk Assessment Reports: France, the Netherlands, Germany.

2. Guidelines for the risk assessment

(Document IV)

A Steering Group of the Scientific Committee, with the support of the staff of the EMCDDA, prepared draft guidelines for risk assessment of new synthetic drugs. This draft was submitted to the Scientific Committee at its plenary meeting of 17 April 1998 and sent also to the institutional participants in the risk assessment. After taking account of their opinions and amendments, the Scientific Committee adopted the draft guidelines at its meeting of 1–2 October 1998 (ST/SCO/9/98 (rev.1)).

In accepting the assignment of risk assessment, the Scientific Committee had adopted some basic principles.

1. The concept of risk will be understood in its dual meaning, which includes both the element of *probability* that some harm may occur (usually defined as 'risk') and the degree of *seriousness* of such a harm (usually defined as 'hazard').
2. The first phase of the scientific risk assessment of a particular drug will be carried out independently of its legal status.
3. Consideration of appropriate measures and of the possible consequences of control of new synthetic drugs will cover a wide range of options and will not necessarily imply prohibition and law enforcement.
4. Scientific evidence on new synthetic drugs will often be limited, so it will be necessary to evaluate the possible risks with reference to similar, known drugs.
5. In the final evaluation the issues of reliability (quality) of information and relevance of the specific risk issues that are involved (health, social risks and consequences of prohibition) should be separately weighted. The final policy consequences of risk assessment will have to be decided within the framework of national or local drug policy priorities.

The meeting having considered the above documentation and comments made by participants adopted the 'Revised Guidelines for Risk Assessment' (Document IV A).

3. Description of MBDB

(Document VIII)

The risk assessment of MBDB has been performed by reference to MDMA because both are usually sold as ecstasy. A review of the scientific literature on MBDB reveals that the data is much more limited than the information available on MDMA which is itself incomplete.

3.1 Chemical description

The meeting noted that MBDB is N-Methyl-1-(1,3-BenzoDioxol-5-yl)-2-Butanamine. It is the α -ethyl homologue of MDMA. MBDB can be synthesised from 1-(1,3-benzodioxol-5-yl)-2-butanone (BDB). BDB can be synthesised from piperonal and 1-nitropropane or 1-bromopropane.

MBDB is synthesised by chemical reactions similar to those used to produce MDMA, but with different precursor chemicals (1-nitropropane or 1-bromopropane) and cannot be produced by accident during attempts to synthesise MDMA. Hence it is synthesised by design from materials which will provide the extra carbon atom which distinguishes MBDB from MDMA.

3.2 Pharmaceutical description

MBDB is mainly sold as tablets for oral consumption and occasionally as capsules or powder. The drug is virtually always sold as ecstasy. It has the same pharmaceutical appearance as MDMA. The logo may be indicative of the content of the tablet, but usually the user is unable to distinguish MBDB from MDMA tablets.

4. Health risks

(Documents V and VIII)

4.1 Individual health risks

(a) Acute effects: The major acute neuropharmacological effects of MBDB in the rat are an increase in serotonin release in the brain and the inhibition of serotonin and noradrenaline re-uptake. These effects compare well with those of MDMA, although the latter is more potent as a re-uptake inhibitor and releaser. MBDB may also slightly increase dopamine release and inhibit dopamine re-uptake, but with a far weaker potency than MDMA. This is important, as dopamine release has been implicated in the serotonin neurotoxicity caused by MDMA and in the reinforcing qualities of substances such as cocaine and amphetamine.

A study using PET scanning techniques in heavy long-term ecstasy users has shown a decrease in a structural component of brain 5-HT neurones.

The few toxicological data available suggest that MBDB may cause serotonergic deficits and neurotoxicity, although the potency of MBDB to cause this effect is smaller than that of MDMA. Severe acute reactions in man as have been reported for MDMA have not been reported for MBDB.

(b) Dependence: Based on animal studies the dependence potential of MBDB appears to be small, probably even smaller than that of MDMA.

(c) Psychological effects: There are little data on the neuropsychological effects of MBDB in man. Neuropsychological findings for MDMA have been described, but these are not necessarily identical for MBDB. Concern has been expressed in one Member State about compulsive patterns of use of ecstasy which have been reported in some studies of heavy consumers. The main subjective effects of MBDB in man are a pleasant state of introspection, with greatly facilitated interpersonal communication and a pronounced sense of empathy and compassion between subjects. In this respect, MBDB again resembles MDMA. However, there are also differences. MBDB has a slower and more gentle onset of action than MDMA, produces less euphoria and has less stimulant properties. The class of substances to which MBDB belongs has been named 'entactogens'.

4.2 Public health risks

(a) Availability and quality: The availability and quality of MBDB across the EU is also hard to assess precisely. Based on the analysis of seizures, only a small proportion of tablets (pills) sold as ecstasy contain MBDB (typically around 1–2%, though this varies over time and between countries, ranging from almost zero to about 5%). In some cases MBDB is the only active ingredient, although on available data it appears more commonly to be combined with other substances (notably 2C-B or MDMA, sometimes LSD or other analogues of MDMA). On the basis of limited information, the typical dose of MBDB is reported to be about 100–130mg, although higher (200mg) and lower amounts are reported.

(b) Knowledge and perception of MBDB among users: There are very limited data on knowledge and perceptions of MBDB. It appears that consumers of ecstasy are often aware that what is sold as ecstasy sometimes contains other substances, but rarely know what those substances are. Apart from the studies of Nichols *et al.* (1986) and Shulgin and Shulgin (1991) there are anecdotal reports from some EU countries of users who were aware that they had taken MBDB. These reports are not entirely consistent and may be based on atypical users, but they generally suggest that MBDB is experienced as having lower stimulant effects as well as lacking the alteration in sensory perceptions associated with MDMA. The predominant impression from these reports is that users prefer MDMA to MBDB, although a few reports reflect more positive reactions to MBDB. It is difficult to interpret these latter reports because the content of the tablets is uncertain, and the characteristics of the users and the effects they were seeking were not reported.

(c) Prevalence and patterns of use: It can be assumed that the patterns of use of MBDB are almost always the same as for MDMA and that the prevalence of (inadvertent) use depends on the extent to which MBDB is present in tablets sold as ecstasy on the market. There appear to be individuals who have consciously used MBDB, but it is probable that these are atypical consumers with a particular interest in, and a sophisticated knowledge of, synthetic drugs. It is also possible that there are local groups of ecstasy users where MBDB has on occasion appeared on the market as MBDB. Since users of MDMA, especially more regular users, are also very likely to consume other drugs (cannabis, alcohol, amphetamines, etc.), MBDB appears to be a very small element in a much wider phenomenon.

(d) Characteristics and behaviours of users: Consumers of MBDB do not differ from users of dance drugs in general. Given the current marginal position of MBDB in the overall pattern of synthetic drug use, it is unlikely that there are any important risk factors or vulnerable groups associated with MBDB in particular.

(e) Indicators of health consequences: There are no reports of emergencies or treatment requests involving MBDB. It is possible that accidents or other episodes involving MBDB, if they occur, are overlooked. However MBDB together with other drugs has been reported in one fatal road traffic accident. It is possible that the lower stimulant effect of MBDB, and the introspective state of mind that it has been reported to induce, might mean that the risk of excessive dancing is reduced. At present no evidence is available on long-term health consequences and possible public health costs.

(f) Context of use: Risks and risk factors linked to the circumstances and rituals of consumption of MDMA include excessive dancing in hot and crowded settings; accidents that may result from sleep deprivation or perhaps direct impairment of driving skills; and also combined use with other drugs (especially alcohol, but also amphetamines, cannabis, LSD and cocaine). It is likely that these apply to MBDB, although to a lesser extent than MDMA.

Because of the scarcity of information on MBDB, the meeting welcomed the integration of bio-medical and socio-economic aspects of drug abuse research in the EC 5th Framework Programme for research and technological development, and hoped that support would be granted to research projects sharing the common objective of developing a coherent and consistent data package on the individual, public health and social consequences of the use of synthetic drugs.

5. Social risks: sociological/criminological evidence (Documents VI and VII)

(a) Social consequences: There is no evidence specifically on MBDB. The available evidence on MDMA does not show any major harmful social consequences for users arising directly from its use, in terms of family or other social relations, problems concerning education,

employment or marginalisation. On the basis of comparison with MDMA, and given that MBDB constitutes a small proportion of the much broader ecstasy market, it is very unlikely that there are any significant harmful social consequences for the user that could be attributed specifically to the use of MBDB.

(b) Consequences for the social behaviour of the user: There is no evidence specifically on MBDB and consequences linked to disorderly conduct, acquisitive crime or violence. However, it might be considered even more unlikely than with MDMA that there is any important link between the use of MBDB and such consequences. The effect on driving is unknown but, as with any drug, is a matter of concern.

(c) Other social consequences: There is no indication that MBDB in particular is associated with any major value conflicts or has any important implications for social institutions beyond those described for MDMA.

(d) Wholesale manufacture and distribution: The Europol contribution confirms the information collected by the Reitox National Focal Points about the current level of small-scale distribution and trafficking of MBDB when compared with other synthetic drugs. Seizures in the European Union have been limited, both in number and quantity, compared with the total number of seized ecstasy tablets. Information from law-enforcement agencies in the Member States has not revealed whether criminal groups specifically manufacture MBDB with a view to avoiding legal controls. Some Member States have indicated the involvement of organised crime in the large-scale manufacture of and trafficking in MBDB.

6. Possible consequences of prohibition

6.1 Legal status

An analysis of the legal status of MBDB in the 15 Member States shows that the drug is controlled in eight of them: Austria, France, Germany, Greece, Ireland, Italy, Luxembourg and the UK. In the Netherlands, it was decided not to prohibit MBDB, after the National Assessment Working Party advised against intervention, but recommended direct monitoring and the evaluation of this decision in due course, or in case of new facts emerging. In some countries, the control on MBDB was adopted through the generic definition of substances within the legislation. In others, MBDB was put under control by analogy of the substance to MDMA.

6.2 Possible consequences of prohibition

The meeting agreed that a discussion on the effects of prohibition should take account of the consequences:

1. to the users of the substance;
2. to the distributors and manufacturers of the substance;
3. to the perceptions and social representations (images) of the substance and its use;
4. to public health issues;
5. to law-enforcement agencies and public security issues;
6. to drug prevention (demand-reduction issues).

For each of these aspects there exist positive as well as negative consequences of prohibition and at the same time the very indecisive data on the substance, its use and its effects were pointed out, so that the discussion of possible consequences is to a certain extent based on speculation. Generally it can be said that there are two obvious scenarios: to prohibit or not to prohibit MBDB; and a third scenario of looking at other possible options of control besides prohibition together with a close monitoring of any adverse effects of not

prohibiting, and to have the possibility of rapid action as soon as any negative developments occur.

- The first scenario would be that the prohibition of this new drug would be a public health preventive measure because of the similarity of MBDB to MDMA. As underlined in the Opinion of the French Commission des Stupéfiants on MBDB, the lack of systematic research of this substance in biological or other samples may possibly create an underestimation of public health problems which could eventually be caused by the new drug. MBDB is not generally recognised as having any therapeutic value and is not only produced industrially.

The prevention of trafficking risks might be another argument to consider, taking into account the essential chemical, pharmacological and toxicological similarity of MBDB to MDMA which is already subject to control, and the hypothesis that the introduction of MBDB in the market was an attempt to substitute MDMA and other substances already placed under control. Different forms of legal status in different Member States could hinder effective international co-operation between law-enforcement agencies. One Member State reported a steep decrease in MBDB seizures after prohibition.

- The second scenario would be to advise against prohibition. The reasons include the relatively low prevalence of MBDB use and supply; evidence suggesting that MBDB is less attractive to users than MDMA; the low involvement of organised crime; as well as expected adverse effects of prohibition like the appearance of new variants. Prohibition was also expected to be an element of criminalisation and marginalisation of – up to now – socially integrated users. This opinion would recommend active monitoring of the market for MBDB and also of the involvement of organised crime, as well as regular evaluation. This scenario includes advice for users and giving information about substances on the market. One Member State reported a significant decrease in MBDB consumption after such a strategy was put into operation.

Another complementary point of view would be to consider that, due to the current lack of evidence of a significant presence of MBDB on the market, the publicity suddenly given to this drug by putting it on a European Union control list might produce an adverse effect. Media focus on a 'new synthetic drug', which had almost 'disappeared' from the market, might provoke moral panic and/ or interest among new users in trying it and might even boost the supply of the drug.

Prohibition was also expected by some experts to hinder or bias research or possible medical uses of the substance, whereas other experts did not expect such a result. It was suggested that another potential effect of prohibition might be to increase the illicit demand for precursors and, hence, to raise the price of those chemicals, with possible consequences on the licit trade and industry.

- Other options would include consideration of a range of measures for control and prevention that fall between full prohibition and non-prohibition. These could be based on a catalogue of measures of control and prevention based on the best practices in this field in Member States. This may be expected to minimise the possible risks associated with the consumption of MBDB, as it is sold as an 'ecstasy-like' dance drug. These options would also envisage a better monitoring of the effects and the trends and patterns of use of these synthetic drugs. In connection with this third approach, the need for further sociological and toxicological research on MBDB was considered necessary.

7. Conclusions

The Scientific Committee of the EMCDDA, extended with experts from the Member States and Representatives of the Commission, Europol and EMEA, are required under Article 4 to draw up a report on all aspects of the Risk Assessment and reflecting all opinions on those aspects

- 7.1 The scientific evidence presented to the meeting shows that MBDB has effects which are similar to those of MDMA, although most studies show that MBDB is less potent than MDMA. However, factors related to dosage and the use of other related drugs might increase the neurotoxicity of MBDB.
- 7.2 Arising from 7.1 and because MDMA is subject to control in Member States, one opinion is that MBDB should be subject to similar measures which would also allow appropriate action by law-enforcement agencies against the manufacture of and trafficking in MBDB.
- 7.3 Also arising from 7.1, a second opinion is to advise against such an intervention for a number of reasons including the relatively low prevalence of MBDB use and its supply and because some evidence suggests that MBDB is less attractive to users than MDMA. This opinion would recommend active monitoring of the market for MBDB and of the involvement of organised crime, as well as regular evaluation of the situation and ongoing research.
- 7.4 The meeting endorsed the view that toxicological data on MBDB are so scarce that any definitive scientific risk assessment would be hazardous. The experts were of the view that to render a risk assessment valid, all kinds of toxic effects should be taken into account including the effects of interaction of other drugs, and that as a priority a toxicological study should be performed in order to identify possible chronic consequences of neurotoxicity.
- 7.5 The expert participants noted that MBDB had been identified in 14 Member States. Information provided to the EMCDDA through the Reitox National Focal Points suggest that MBDB is almost always sold and consumed as ecstasy. Users are aware that different ecstasy tablets may have different effects. In most cases they do not attribute these differences specifically to MBDB. Anecdotal reports from some Member States suggest that MBDB may not be as attractive as MDMA to users.
- 7.6 No specific evidence of social risks directly linked to MBDB have been reported. This is probably also due to the fact that it does not have a separate identity as a product on the market or within the reporting mechanism in some Member States.
- 7.7 The meeting noted that indications from Europol did not point to a high level of manufacture of, trafficking in and involvement of organised crime with MBDB when compared with other synthetic drugs. It was pointed out that the total number of MBDB tablets seized in the European Union was relatively low compared with the total number of seized ecstasy tablets. It was further noted that MBDB had no generally recognised or accepted medical, pharmaceutical or industrial use.
- 7.8 A matter of concern may be the fact that the main precursor chemicals of BDB which may be used in the synthesis of MBDB are widely and commercially available:
 - piperonal, commonly used in the perfumes industry; at the EU level, piperonal is included in the Regulation (EEC) no. 900/92 of 31 March 1992 modifying the Regulation (EEC) no. 3677/90 related to measures to be taken to prevent the diversion of a number of substances for the illicit manufacture of narcotics and psychotropic substances in third countries. Directive (EEC) no. 109/92 deals with similar controls relating to the Internal Market.
 - 1-bromopropane and 1-nitropropane, two high-volume chemicals (production exceeding 1 million pounds in the US). These substances are not under the same regulation as piperonal, safrole, isosafrole and other precursors commonly used in the manufacture of synthetic drugs.

Lisbon, 10 November 1998

Suggestions made by the meeting on the risk assessment of MBDB concerning measures for improving the risk assessment of new synthetic drugs in the future

The meeting noted with concern, and wishes to draw the attention of the Member States and the European institutions to, the general lack of information on important parameters relating to the health and social risks and the possible consequences of prohibition of MBDB:

- The meeting emphasised the need for information on the chronic effects of neurotoxicity and on the general toxicity of MBDB. In this regard, the possible long-term psychiatric consequences of MBDB and related drugs should be studied.
- The meeting agreed with the need for basic monitoring of drugs on the market, for information on patterns of use and reported effects, and for research on the impact on driving.
- The meeting suggested that the Scientific Committee of the EMCDDA should give further consideration, within the context of Articles 3 and 4, to improving risk-assessment methodology in this field including criteria for allocating scores and weighting the evidence.
- The meeting suggested to the European Commission, the European Council and to the Member States that, in the event of further risk assessment of new synthetic drugs under the Joint Action, a more complete data package should be developed which would make the assessment more scientifically rigorous.
- The meeting recommended that, when a new synthetic drug is notified for risk assessment, and where preliminary research shows it to be necessary, that a supply of that drug be obtained from a validated recognised producer and that a laboratory with recognised expertise in toxicology testing be contracted to provide standard toxicity data of a quality comparable (as far as is practicable) to that used in the risk assessment of other chemical compounds within the European Union. An inventory of suitable laboratories within the EU should be prepared.

Lisbon, 10 November 1998