INVITED REVIEW

N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB): its properties and possible risks

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Abstract
MBDB (N-methyl-1-(1,3-benzodioxol-5-yl)-2-aminobutane) is the α-ethyl homologue of MDMA (3,4-methylenedioxy-N-methylamphetamine). MBDB is metabolized and excreted similarly to MDMA: presumably, the majority of oral MBDB is excreted in urine unmetabolized. The main metabolic routes in man are thought to be O-dealkylation and subsequent methylation, sulphation and glucuronidation of the newly formed hydroxy groups. The major acute neuropharmacological effects of MBDB in the rat are an increase in serotonin release in the brain and an inhibition of serotonin and noradrenaline re-uptake. These effects compare well with those of MDMA, although the latter is more potent. MBDB may also slightly increase dopamine release and inhibit dopamine re-uptake, but to a lesser extent than MDMA. This is important, as dopamine release has been implicated in the reinforcing qualities of substances such as cocaine and amphetamine. The neuroendocrine effects of MBDB resemble those of MDMA. Both substances increase plasma ACTH, corticosterone, prolactin and renin. The neurophysiological effects of MBDB are characterized by a decrease in electrical activity throughout the brain, most notably in the alpha 2 and delta frequency bands. In contrast, hallucinogens increase the activity in the alpha 1 band, especially in the corpus striatum. In drug discrimination tests in the rat, MBDB, like MDMA, can be distinguished clearly from both stimulants and hallucinogens. The class of substances to which MBDB belongs may be named entactogens. MBDB dose-dependently increases locomotor activity and decreases exploratory behaviour in the rat and causes distress vocalization and wing extension in the newly hatched chicken. The rewarding properties of MBDB appear to be smaller than those of MDMA, as suggested by a 2.5 times weaker potency in the conditioned place preference test in rats. 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 few toxicological data available suggest that MBDB may cause serotonergic deficits in the brain, although the potency of MBDB to cause this neurotoxic effect is smaller than that of MDMA. Severe acute reactions in man as have been reported for MDMA have not been published for MBDB. The dependence potential of MBDB appears to be small, probably even smaller than that of MDMA. MBDB has been available at least since 1994 but its position on the synthetic drugs market is marginal. Subjective reports indicate that MBDB largely lacks the stimulant properties of MDMA. We calculated a margin of safety with a method similar to one used in the risk assessment of pharmaceuticals. The results suggest that MBDB is three times less likely to cause serotonergic brain deficits than MDMA. However, it should be noted that for both substances the margin of safety is less than one, indicating that the risk of neurotoxicity is not negligible. In animals, serotonergic brain deficits after exposure to MDMA have been linked to the degeneration of serotonergic nerve terminals.

Introduction

Much has been done to clarify the mechanism of the pharmacological actions and toxicity of 3,4-methylenedioxymethylamphetamine (MDMA, “ecstasy”). Even though substantial progress has been made, we still do not know exactly how MDMA works and how risky the use of this substance is. Compared with MDMA, N-methyl-1-(1,3-benzodioxol-5-yl)-2-aminobutane (MBDB) has received little attention from the scientific community. Therefore, our understanding of the pharmacological and toxicological actions of MBDB is much smaller, and the risks of consuming MBDB are even harder to estimate than for MDMA. In this report, the scientific knowledge on MBDB will be reviewed. The MBDB data will be compared with those for MDMA, which is similar in structure and action. For a more thorough review of the properties and effects of MDMA, the reader is referred to three recent publications.1-3

The data on MBDB reviewed here have been used by the Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) for the risk assessment on MBDB within the framework of a Joint Action adopted by the Council of the European Union on 16 June 1997.14 This Joint Action on New Synthetic Drugs aims to:

- provide for the establishment of an early-warning system to identify new synthetic drugs as they appear on the European market;
- incorporate a mechanism for assessing the risks of these drugs; and
- comprise a decision-making process through which these products may be placed under control in the EU Member States.

In addition, we present at the end of this paper a method for risk assessment of health risks associated with the use of MBDB. The purpose of this assessment is to illustrate how scientific knowledge can be used to evaluate the risks of non-medically used psychoactive drugs.

Chemical description

MDMA is short for 3,4-methylenedioxymethylamphetamine it could also be named N-methyl-1-(1,3-benzodioxol-5-yl)-2-aminopropane. The molecular structure is shown in Fig. 1. The main precursors for synthesizing of MDMA are piperonylmethylketone, piperonal, safrole and isosafrole. MBDB is N-methyl-1-(1,3-benzodioxol-5-yl)-2-aminobutane (Fig. 1). It is the α-ethyl homologue of MDMA. The free base is a colourless oil with a melting point of 88°C at 0.08 mm Hg. The hydrochloride salt consists of colourless crystals with a melting point of 156°C.5 Nuclear magnetic resonance data were reported by Nichols and co-workers.5 MBDB can be synthesized from 1-(1,3-benzodioxol-5-yl)-2-aminobutane (BDB). The extra carbon atom in this precursor compared with MDMA precursors prevents MBDB
from turning up by accident when one attempts to synthesize MDMA or vice versa. BDB is not commercially available. It can be synthesized from piperonal and 1-nitropropane or 1-bromo-propane. MBDB can be analysed with gas chromatography/mass spectrometry (GC/MS). With these methods, MBDB can be distinguished from congeners such as MDMA, 3,4-methylenedioxy-N-ethylamphetamine (MDEA) and 3,4-methyle-nedioxyamphetamine (MDA).6 ± 9

**Pharmaceutical form**

MDMA is mainly sold as tablets, and occasionally as capsules or powders. Tablets often show distinctive markings (logos). MDMA is traded under the name ecstasy (XTC). MBDB is virtually always sold as “ecstasy” (Table 1). It has the same pharmaceutical appearance as MDMA (Table 2). The logo may be indicative of the content of the tablet, but the dynamics of the ecstasy market are such that these markings may become misleading.10 Therefore, MBDB should be considered an integral part of the ecstasy market.

**Route of administration and dosage**

As a rule, MDMA is ingested. Accounts of intravenous administration or snorting of this drug are rare. Typical doses taken orally range from 50 to 150 mg. Although many users take single doses, multiple dosing is not uncommon. Many users concomitantly use other psychoactive substances, such as tobacco, alcohol, cannabis, amphetamine and LSD.

MBDB is also taken orally. Shulgin & Shulgin11 and Nichols and co-workers5 reported on consumption of 150–210 mg, and MBDB containing street samples analysed by Rothe and co-workers9 contained, on average, 197 mg. In contrast, most Member States reported to the EMCDDA that the mean amount of MBDB found in tablets is about 100 mg.

**Pharmacodynamic properties and preclinical safety data**

**Neuropharmacology**

The major acute neurochemical effects of MBDB in the rat are an increase in serotonin release in the brain and an inhibition of serotonin and noradrenaline re-uptake. The drug may also slightly increase dopamine release and inhibit dopamine re-uptake. All the evidence reviewed in this paragraph is from studies in the rat. The acute effects of MBDB on serotonin in the rat brain are similar to those of MDMA, the latter being somewhat more potent in most models. MBDB and MDMA were equally potent in releasing serotonin in vitro in slices from the

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<th>Table 1. MBDB-containing tablets identified by the Drug Information and Monitoring System</th>
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Names under which the tablets were sold (1994–June 1998).
hippocampus in rat brain.\textsuperscript{12} \textit{In vivo}, MBDB (25 mg/kg) and MDMA (20 mg/kg) comparatively reduced the level of serotonin and its metabolite 5-HIAA (5-hydroxyindoleacetic acid) in the frontal cortex 3 hours after an intraperitoneal (i.p.) injection.\textsuperscript{13} A lower dose of racemic MBDB given subcutaneously (s.c.) (5 mg/kg) also decreased the level of serotonin and 5-HIAA in the frontal cortex, this time measured 40 minutes after injection. S-MDMA (3 mg/kg, s.c.) had the same effect.\textsuperscript{14}

Inhibition of serotonin re-uptake has been shown \textit{in vitro}, using nerve cell synapse samples from the hippocampus\textsuperscript{15} or from a mixture of cortex, hippocampus and caudate nucleus tissue.\textsuperscript{16} In these experiments, MBDB was about half as potent in inhibiting serotonin re-uptake (IC\textsubscript{50} 0.8 \(\mu\text{M}\)) as MDMA (IC\textsubscript{50} 0.4 \(\mu\text{M}\)).\textsuperscript{16} Stereoselectivity was found for the re-uptake inhibition in hippocampal samples, the S-isomer being the most active.\textsuperscript{13} The apparent re-uptake inhibition could be attributed in part to the serotonin releasing effect of MBDB.\textsuperscript{16}

In conclusion, MBDB increases the release and inhibits the re-uptake of serotonin in the brain of the rat, albeit with lesser potency than MDMA.

The acute effects of MBDB on brain dopamine are weaker than those of MDMA. MDMA, but not MBDB, increased the release of dopamine in superfused rat hippocampal brain slices.\textsuperscript{12} Also unlike MDMA, MBDB failed to raise dopamine levels in the frontal cortex 3 hours after i.p. injection.\textsuperscript{15} A low dose of racemic MBDB (5 mg/kg, s.c.) was without effect on the dopamine level in the frontal cortex of the rat 40 minutes after injection, in contrast to S-MDMA (3 mg/kg, s.c.).\textsuperscript{14} In \textit{in vivo} microdialysis studies in awake, freely moving rats, a single injection of MBDB (21 mg/kg, i.p.) raised extracellular dopamine concentrations in the striatum 60 and 90 minutes after injection, but this elevation was smaller and of shorter duration than the one seen after injection of an equimolar dose of MDMA.\textsuperscript{17} Administration of a low dose of MDMA (6.3 mg/kg, i.p.) increased extracellular concentrations of dopamine and its metabolite DOPAC in the nucleus accumbens as measured with microdialysis probes, but MBDB (7 mg/kg, i.p.) did not.\textsuperscript{18} The slight increase in dopamine release may be explained by metabolism of MBDB to \(\alpha\)-ethylepine (\(N\)-methyl-1-(3,4-dihydroxyphenyl)-2-butanamine), which releases non-vesicular dopamine.\textsuperscript{16}

\textit{In vitro}, neither enantiomer of MBDB inhibited the re-uptake of dopamine to 50\% of the controls in striatal synaptosomes when tested up to 5 \(\mu\text{M}\).\textsuperscript{15} However, in mixed cortical/hippocampal/caudate nucleus synapse samples re-uptake of dopamine was inhibited by racemic MBDB (IC\textsubscript{50} 7.8 \(\mu\text{M}\)), but with far (six times) lesser potency than MDMA.\textsuperscript{16} As for serotonin, the apparent re-uptake inhibition by MBDB could be attributed in part to the release of non-vesicular dopamine.\textsuperscript{16} Thus, MBDB may increase the release and inhibit the re-uptake of dopamine in the brain of the rat, but the potency of MBDB is far less than of MDMA. This is important, as dopamine release has been implicated in the serotonin neurotoxicity of MDMA\textsuperscript{2,19} (see also Toxicology, below) and in the reinforcing qualities of substances such as cocaine and amphetamine\textsuperscript{12,17} (Dependence Potential, below).

MBDB affects noradrenaline systems in rat brain. In \textit{vivo}, MBDB inhibited re-uptake of noradrenaline in hypothalamic\textsuperscript{15} and mixed cortical/hippocampal/caudate nucleus synapse samples (IC\textsubscript{50} 1.23 \(\mu\text{M}\)), but less so than MDMA (IC\textsubscript{50} 0.41 \(\mu\text{M}\)).\textsuperscript{16} Stereoselectivity was found for the re-uptake inhibition in hippocampal samples, the S-isomer being the most active.\textsuperscript{15} In \textit{in vivo} experiments, both MDMA (20 mg/kg, i.p.) and MBDB (25 mg/kg, i.p.) did not reduce the tissue levels of noradrenaline in the cortex 3 hours after injection.\textsuperscript{13} Thus, MBDB inhibits the re-uptake of noradrenaline in the brain of the rat, albeit with a lesser potency than MDMA.

\textbf{Neuroendocrinology}

MBDB profoundly affects the secretion of hormones in the rat, the only species studied so far in this respect. MBDB dose-dependently (5–10 mg/kg, i.p.) raised the plasma adrenocorticotropic hormone (ACTH), corticosterone, prolactin and renin.\textsuperscript{20} These effects could be blocked by the selective serotonin re-uptake inhibitor fluoxetine, suggesting that MBDB influences the secretion of these hormones through serotonin by interaction with the serotonin re-uptake carrier.\textsuperscript{20} MBDB (5 mg/kg, i.p.), and two other serotonin-releasing agents (MMAI and MTA), also decreased blood pressure and heart rate in the rat.\textsuperscript{20}

The neuroendocrine effects of MBDB resemble those of MDMA.\textsuperscript{21–24} However, subtle differences between MDMA and MBDB may exist. For example, the MDMA-induced prolactin
secretion was not blocked by fluoxetine. What strikes most, however, are yet again the similarities in action between MDMA and MBDB. Both substances increase plasma ACTH, corticosterone, prolactin and renin in the rat. The effects of MDMA on ACTH, cortisol and prolactin have also been demonstrated in man. In rats that were pretreated with MDMA, an altered response of ACTH and prolactin to a fenfluramine challenge can persist for months. Similarly, MDMA users that were MDMA abstinent for at least 3 weeks showed a diminished cortisol and prolactin response to a fenfluramine challenge when compared with control groups. Recently, MDMA has been found to affect the release of vasopressin in man. It is not known if these neuroendocrine effects in humans are shared by MBDB. However, since these effects are mainly serotonin-mediated, it may be expected that MBDB similarly disrupts the human neuroendocrine system.

Neurophysiology
Dimpfel and co-workers studied the neurophysiological effects of S-MDB (1.6 and 2.4 mg/kg), S-MDB (0.4; 0.8; 1.6 and 2.4 mg/kg) and S-amphetamine (0.2 and 0.4 mg/kg) and the hallucinogens R-DOH (0.1 mg/kg), R-DOB (0.2 mg/kg) and R-DOI (0.1 mg/kg) on brain field potentials in the freely moving rat. Recordings were made in the frontal cortex, hippocampus, striatum and reticular formation for 2 hours after drug administration. In terms of spectral patterns, the changes seen after injection of MBDB, MDMA and amphetamine were similar. The spectral patterns after injection of the non-hallucinogens were characterized by a decrease in electrical activity throughout the brain, most notably in the alpha2 and delta frequency bands. One exception was the decrease in theta activity in the frontal cortex, which was more gradual for MBDB than for amphetamine, whereas MDMA even increased theta activity in the frontal cortex for 45 minutes after injection. In contrast, the hallucinogens increased the activity in the alpha1 band, especially in the striatum. The authors related the increase in activity of the alpha1 frequency band to the property of hallucinogens to activate 5-HT2A (serotonin) receptors. The authors suggested that dopaminergic mechanisms were responsible for the spectral decreases caused by the non-hallucinogens. This proposal is unlikely, as MBDB does not strongly influence dopamine release or re-uptake (see Neuropharmacology, above).

Behavioural effects in animals
When administered subcutaneously, racemic MBDB dose-dependently (5 or 10 mg/kg) increased locomotor activity and decreased exploratory behaviour in the rat. The effects on locomotor activity do not simply reflect the dopamine- and serotonin-releasing or re-uptake-inhibiting properties of MBDB and other phenylalkylamines, or their hallucinogenic potential. S-MDB also changed locomotor activity when injected into the nucleus accumbens, suggesting that dopamine or noradrenaline release in the nucleus accumbens mediates the behavioural effects of this drug. However, racemic MBDB was without effect when injected into this part of the brain. Perhaps MBDB may influence locomotion indirectly through 5-HT1 (serotonin) receptors.

In another model, newly hatched chickens were injected with a drug. Both hallucinogens and stimulants such as amphetamine caused the birds to squeak (distress vocalization) and spread their wings. An abnormal body posture suggested that the drug had hallucinogenic properties, while amphetamine resulted in loss of the righting reflex. In this test, MBDB dose-dependently caused non-discriminative distress vocalization and wing extension. Only at the highest dose given (24 mg/kg) were abnormal body posture and loss of righting reflex seen. Thus, the drug would not appear to be a marked hallucinogen or stimulant. The N-desmethyl homologue BDB was more potent than MBDB, whereas the N,N-dimethylated variant N,N-dimethyl-1-(1,3-benzodioxol-5-yl)-2-aminobutane (MMDB) had no effect.

Drugs may be consumed because of their rewarding properties. A method to assess possibly rewarding effects of substances in animals is the conditioned place preference (CPP) test. In this paradigm, drugs are tested for their ability to induce an animal to prefer a site that it disliked under control conditions. MBDB was about 2.5 times weaker than MDMA in rats in the CPP test. The effective dose in this respect does not greatly affect dopamine release. Therefore, it is far from certain that dopamine release accounts for the weak rewarding effect of MBDB.
Subjective effects in man

In an early study 29 subjects were referred by psychotherapists or friends for a so-called MDMA session. The drug made the subjects feel more close and intimate with all those present: they were more communicative, more open to compliments or criticism and they generally appreciated the changes in mood and emotions. One subject became fearful during the session and had anxiety attacks a few weeks later, but he felt that this was caused by earlier events in his life, with MDMA releasing tightly controlled emotions.

The main psychological effects of MDMA in healthy volunteers with no experience with this drug were an increase in mood, well-being and emotional sensitivity. There was some anxiety, but hallucinations and panic reactions were not noted. Mild depersonalization and derealization phenomena did occur, together with moderate thought disorder, first signs of loss of body control and alterations in the meaning of perceptions. Subjects also displayed changes in the sense of space and time, heightened sensory awareness and increased psychomotor drive.

Racemic MBDB was tested in 14 subjects, of both sexes, ranging in age from 35 to 60 years. They all had experience with a wide variety of psychoactive substances. Effective doses of racemic MBDB were in the range of 150–200 mg. An effect was noted in some individuals within 20 minutes of administration of the drug. For most, however, it took 30 ± 45 minutes before a clear change was observed. In contrast to hallucinogens, MBDB’s effect was subtle and gentle in onset.

The drug produced a pleasant state of introspection, with greatly facilitated interpersonal communication. Subjects could talk readily about emotionally painful past events if they wished, without apparent embarrassment or inhibition. There was a pronounced sense of empathy and compassion between subjects. After reaching a maximum between the first and second hour after ingestion, MBDB’s action gradually tapered off. The effect lasted approximately 5 hours. Subjects felt able to sleep or drive an automobile and to function normally by that time. There were no visual distortions or hallucinations. However, some subjects did report mild nystagmus. There was no closed-eye imagery, even in a darkened room. The subjects agreed that MBDB did not resemble a hallucinogen.

In the study by Nichols and co-workers all subjects were familiar with MDMA. They found MBDB and MDMA to be generally similar in effect, with two exceptions. First, the onset of action of MBDB was slower and more gentle than for MDMA; there was little of the anxiety that sometimes occurs as soon as MDMA takes effect. Secondly, MBDB seemed to produce less euphoria than MDMA. In a double-blind, placebo-controlled cross-over study with four subjects, S-MBD (125 mg, orally) was more active than the same dose of R-MDB. MDMA has the same stereoselectivity of action. These subjects knew the effects of stimulants such as amphetamine and methylphenidate, and felt that MBDB was different. MBDB usually made them sit or lie quietly.

The picture emerging from users’ comments, gathered by Shulgin & Shulgin, is in keeping with the experimental data. The subjective effects of 210 mg MBDB, sometimes supplemented with 50 or 70 mg close to 2 hours after the first dose, were like those experienced with MDMA. However, there are minor differences. Notably, people taking MBDB were more relaxed, felt more quiet, had lesser drive and less inclination to talk, and were less stimulated than with MDMA. They also experienced very little visual activity.

In summary, the main subjective effects of MBDB 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 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.

MBDB is an entactogen

In the drug discrimination test, an animal (usually a rat) is conditioned to respond, for instance pressing the left of two levers if given a drug, and the right one if given a placebo. Drug-appropriate responding occurs either after administration of the training dose of the original drug or when a new drug is perceived by the animal to be similar (substitution). In the rat, MDMA and MBDB did not substitute for LSD or for S-amphetamine. Conversely, when S-MBDB was used as the training drug, only partial substitution occurred when the hallucinogens LSD, DOM and mescaline, or the stim-
ulants S-amphetamine, S-methamphethamine and cocaine were tested. On the other hand, with S-MBDB as the training drug, complete substitution was seen for racemic, S- and R-MDMA, and when racemic MDMA was used as the training drug complete substitution took place with both enantiomers of MBDB. Apparently, MBDB and MDMA are alike in many respects. These substances may be representatives of one and the same class of psychoactive compounds, distinct from both hallucinogens and stimulants. This class may be named “entactogens”, from the Greek roots en for within and gen for to produce or originate, and the Latin root tactus for touch. Hence the connotation of this word is that of drugs “producing a touching within”. In contrast to S-MBDB, racemic MDMA could be substituted for completely by S-amphetamine, although at high doses. This confirms subjective reports that MBDB has less stimulant properties than MDMA. In other words, whereas MDMA is an entactogen with some stimulant properties, MBDB may be an entactogen pur sang. In conclusion, rats can distinguish both MBDB and MDMA from stimulants and hallucinogens in drug discrimination tests. The class of substances to which MBDB belongs may be named entactogens.

Toxicology

MDMA reduces serotonin neuronal markers in the brains of rodents and non-human primates. These changes may be due to neurodegenerative processes of terminals of serotonergic neurones in the dorsal raphe nucleus. Altered serotonin innervation patterns have been found in the forebrain of monkeys treated with MDMA 7 years earlier. When polydrug users who had taken ecstasy on multiple occasions were subjected to positron emission tomographic imaging, they showed reduced serotonin re-uptake site density when compared with a control group without any experience with MDMA. The nature and the scope of any functional consequences of these serotonergic deficits are still unclear. Occasionally, people using this drug develop mental disorders such as psychosis, depression and anxiety disorders. It is not known whether these disorders are caused directly by MDMA, the result of pre-existing morbidity aggravated by MDMA, or unrelated to the use of this drug. Recent findings suggest that cognitive and personality changes are not uncommon in users of MDMA. They are somewhat impaired in memory tasks and in impulse control.

Until now, the neurodegenerative effects of MBDB have only been evaluated in the rat. When rats were injected with racemic MBDB (25 mg/kg, i.p.) twice a day for 4 consecutive days, tissue levels of serotonin and its metabolite 5-HIAA were reduced in the cortex and the hippocampus 2 weeks later. Also, the density of serotonin re-uptake sites in the cortex was reduced. Although no further characterization of the neurotoxic effects of MBDB has been undertaken, these findings suggest that MBDB may have neurotoxic properties similar to those of MDMA. There may, however, be a difference in potency. Unlike MDMA (20 mg/kg, i.p.), a single dose of MBDB (21 mg/kg, i.p.) did not reduce tissue serotonin and 5-HIAA levels in the striatum in the rat brain 7 days after treatment, and the reduction of the serotonin neuronal markers in the cortex and hippocampus 2 weeks after multiple dosing (25 mg/kg, i.p.), twice a day for 4 days) was smaller than after a comparable treatment with MDMA (20 mg/kg). Thus, on an equimolar basis the neurotoxic potential of MBDB is smaller than that of MDMA.

It has been proposed that one step in the neurotoxic mechanisms of MDMA is the ability of the drug to release dopamine. As mentioned above, MBDB is much weaker in releasing dopamine than MDMA. Therefore one may argue that MBDB is less neurotoxic because it is less potent to release dopamine. However, the hypothesis that dopamine plays a key role in MDMA-induced neurotoxicity has been questioned recently. Other factors, such as the hyperthermic effect of MDMA, its ability to form neurotoxic metabolites and its facilitatory effect on the formation of free radicals, leading to oxidative damage, may be more important and do not necessarily depend on the drug’s ability to release dopamine.

Combining MBDB with other substances may affect the neurotoxicity of MBDB. Co-administration of the serotonin releasing MDMA analogue 5,6-methylenedioxy-2-aminoindan (MDAI) with d-amphetamine reduced serotonin neuronal markers in the rat brain 1 week later, whereas neither of these two substances did so when given alone. Simultaneous intake of amphetamine and MBDB by recreational drug users is quite conceivable. Many ecstasy users
also use other drugs, including amphetamine. Also, tablets purchased as ecstasy may contain MBDB as well as amphetamine, although this combination is rare according to the Dutch drug supply monitor (see “Pharmaco-epidemiology” below).

Apart from the few data on the neurotoxicity of MBDB, nothing is known about any other toxicity of MBDB. To our knowledge, no further toxicological investigations with animals have been performed. MDMA may cause severe adverse reactions, including death. MDMA-induced hyperthermia plays a pivotal role in most of these reactions. Other serious complications associated with the use of MDMA are arrhythmia and hepatotoxicity. There are no reports that any of these adverse effects, or other complications, also occur when MBDB is used. However, this drug is not as readily available as MDMA, or users may not be aware that the tablets they ingested contained MBDB. Fatal arrhythmia after the use of MDMA is thought to result from the stimulant effect of MDMA, leading to hyperactivity, combined with pre-existing cardiovascular morbidity. Since MBDB has hardly any stimulant properties, this drug is unlikely to precipitate arrhythmia. In summary, the few data available suggest that, like MDMA, MBDB can cause serotonergic deficits in the brain, although the neurotoxic potency of MBDB is smaller than that of MDMA. Severe acute reactions as have been reported for MDMA have not been documented.

Dependence potential
The consumption of some psychoactive substances may lead to dependence. Among other things, this risk is related to the reinforcing effects of the drug. The rewarding potential of MDMA is believed to result from the release of dopamine in the nucleus accumbens. MBDB also releases dopamine, but only marginally. The weak potency of MBDB to release dopamine could perhaps explain why this drug largely lacks the reinforcing qualities of such substances as cocaine and amphetamine. Subjective reports indicate that MBDB produces less euphoria than MDMA. MBDB may not be completely free of dependence potential, however. As discussed above, MBDB is active in the CPP test in rats, although much less than MDMA. Taken together, these data suggest that MBDB is not as rewarding as cocaine and amphetamine or even MDMA. Thus, the dependence potential of MBDB is likely to be small, probably even smaller than that of MDMA.

Pharmacokinetic properties in man
MBDB taken as a single oral dose of 100 mg was detectable by GC/MS in the urine of a volunteer for 36 hours. The urine concentration of MBDB peaked at 4 hours, and there was a second, unexplained smaller peak (10% of the first) at 22 hours after ingestion. A similar excretion pattern was seen in a volunteer who had taken an oral dose of 50 mg MDMA. In that case, approximately two-thirds of the MDMA was excreted unmetabolized. MBDB concentrations in the urine samples from 10 people suspected of petty drug offences were in the same range as those reported by Kintz. Kronstrand also found BDB in these urine samples. In all the studies cited, the analysis of the urine samples did not include a hydrolysis step. It is known that conjugated metabolites are not detected if a hydrolysis step is omitted. The predominance of conjugated O-dealkylated metabolites may therefore have been obscured.

The phase I metabolism of methylenedioxyphenylalkylamines, such as MBDB, may consist of two parallel routes. One of these is opening of the methylenedioxy ring leading to O-dealkylation and leaving two hydroxy groups attached to the phenyl ring. Subsequent methylation of one of the hydroxy groups leads to the formation of a methoxy derivative. The other route involves degradation of the side chain to the N-dealkyl and, subsequently, deamino-oxo metabolites. The O-dealkylated methoxy metabolites are sulphated and/or glucuronidated in phase II reactions. The benzoic acid derivative of MDMA formed by the side-chain degradation can be further metabolized to its glycine conjugate. In contrast, glycine conjugation of the MBDB-derived benzoic acid metabolite has not been reported. The cytochrome P450 isoenzyme CYP2D6 catalyses the first step in the O-dealkylation route. The O-dealkylation metabolic route is thought to be predominant in man, but because of the known genetic poly-
morphism in Caucasians for CYP2D6 inter-individual differences in metabolism of MBDB in humans are likely to exist.

Pharmacoepidemiology
Information from the Member States collected by the EMCDDA confirms that MBDB is usually sold as ecstasy. Therefore, MBDB will not turn up in its own right in epidemiological surveys. The data we have on the availability of MBDB on the illicit drug market come mainly from other sources, such as drug seizures and drug supply monitors.

MBDB was found in hair samples of two of 20 regular ecstasy and “speed” users from the techno-music scene in Germany. The period of taking the drug had presumably been brief. In the same study, MBDB was only seen in 3 of 127 ecstasy tablets. The average amount of MBDB in these tablets was 197 mg. In most Member States’ reports to the EMCDDA an average quantity of about 100 mg MBDB per tablets is mentioned.

In Sweden, MBDB was identified in routine analysis of a urine sample from a person suspected of a petty drug offence. After the first sample, approximately 4000 samples were negative, but than again in a 2-month period nine more samples were confirmed positive. Data from the Netherlands come from the Drugs Information and Monitoring (DIMS) project, a so-called supply monitor. Drug users voluntarily and anonymously hand in a drug sample at one of the participating institutions for addiction care. These samples are analysed in a laboratory. One week later the person is notified of the contents of the sample and he is also educated on the possible health risks of the drug(s) involved. Also, DIMS may issue warning campaigns. Between 1993 and 1998, 10 540 tablets were analysed. In the last 4 years, the yearly proportion of “ecstasy” tablets containing MBDB was never higher than 4%, and mainly around 1% (Table 3).

MBDB has been available at least since 1994. Nevertheless, its position on the synthetic drugs market is marginal. From subjective reports it appears that MBDB is less popular among users than MDMA. The reason for this may be that MBDB produces less euphoria than MDMA. Another possible explanation is that MBDB largely lacks the stimulant properties of MDMA.

Risk assessment of MBDB as a model for other non-medically used psychoactive substances
The purpose of this section is to further the discussion on how risk assessment of non-medically used psychoactive substances can be undertaken. Such a risk assessment involves many issues. Not only the health risks for the individuals taking a particular drug, but also the impact the use of this drug may have on public health and society as a whole need to be evaluated. One way in which health risks can be assessed will be discussed here and applied to MBDB and MDMA, for the purpose of illustrating the method.

Using a margin of safety
Risks are taken voluntarily by all of us every day. A well-known example of “chemical” risks is the self-administration of medicines. Toxicological risk assessment of a potential medicine starts with extrapolation of insights and data from animal experiments. The first step is to estimate the levels of exposure at which specified adverse effects may occur in man. Then the chances that these adverse effects take place are weighed against the therapeutic gain to be expected when using the medicine. This results in a margin of safety. Depending on the size of the therapeutic gain expected, the intended availability of the substance (e.g. prescription or over-the-counter drugs), the nature and severity of the toxic effects and other factors, varying levels of the margin of safety may be set as acceptable. The margin of safety is defined as the ratio of the therapeutic dose and the predicted NOAEL in man (as derived by extrapolation from animal data). No Observed Adverse Effect Level, i.e., the highest dose of a substance at which no adverse effect was found. Ideally, animal and human data should be compared on the basis of systemic exposure, for which pharmacokinetic measures are needed, usually the area under the curve (AUC) of a curve of the drug concentration in plasma against time, or the maximal concentration reached in plasma (C_max). If these pharmacokinetic data are wanting, allometric scaling may be applied, meaning that animals and man are compared using established relationships between body weight and pharmacokinetic parameters. However, this may not be appropriate when a drug is largely eliminated by hepatic metabolism.
Table 3. Contents of MBDB-containing tablets identified by Drug Information and Monitoring System

<table>
<thead>
<tr>
<th>Year</th>
<th>MBDB only</th>
<th>MBDB + 2CB</th>
<th>MBDB + MDMA</th>
<th>MBDB + caffeine</th>
<th>MBDB + amphetamine</th>
<th>MBDB + MDMA</th>
<th>MBDB + MDEA</th>
<th>MBDB + caffeine</th>
<th>MBDB + unknown</th>
<th>Total MBDB (number)</th>
<th>Total MBDB (% of all tablets analysed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>1995</td>
<td>21</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>30</td>
<td>2</td>
<td></td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>1996</td>
<td>8</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>24</td>
<td>2</td>
<td>&lt;1</td>
<td></td>
<td>24</td>
<td>&lt;1</td>
</tr>
<tr>
<td>1997</td>
<td>25</td>
<td>52</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>95</td>
<td>4</td>
<td>95</td>
<td>4</td>
</tr>
<tr>
<td>1998 1–6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Such a margin of safety could also be used for non-medically used psychoactive drugs. The definition of this margin of safety would be the ratio of a recreational dose and the predicted NOAEL in man. In analogy to practice in pharmaceutical industry, 2 could be set as the margin of safety below which the health risks are considered to coincide with the intended effect. A margin of safety of 10 or above would be acceptable. For a final judgement on the acceptability of margins of safety between 2 and 10, additional factors would need to be weighed, such as the frequency of use of the substance and the severity of the possible adverse health effects.

As for MBDB, the only NOAEL that can be derived from existing animal data is the one reported by Nash & Nichols\(^1\)\(^,\)\(^1\)\(^7\) with regard to the lack of a reduction of serotonin neuronal markers in the rat striatum after a single dose of 21 mg/kg MBDB. Extrapolation of this NOAEL to man, using allometric scaling, would yield a predicted NOAEL of 2.1 mg/kg. Since the recreational dose of MBDB in man is 2.1–2.9 mg/kg\(^5\)\(^,\)\(^1\)\(^1\), this would result in a margin of safety of 0.75–1. This means that if MBDB-induced neurotoxicity occurs in man as it does in rats, recreationally taken doses are likely to adversely affect at least some of the users.

The same method can be applied to MDMA, with regard to the same parameter (reduction of brain serotonin neuronal markers). In one study, squirrel monkeys were given 2.5 mg/kg MDMA twice monthly for 4 months by the intragastric route (G. Ricaurte, unpublished observations). Serotonin or 5-HIAA levels did not change in eight brain regions. However, a single oral administration of 5 mg/kg reduced serotonin in the thalamus and hypothalamus in this primate.\(^5\)\(^7\) Thus, as far as the reduction of brain serotonin neuronal markers is concerned, 2.5 mg/kg is the NOAEL in the squirrel monkey.

In rhesus monkeys given MDMA orally twice daily for 4 consecutive days, serotonin was reduced in the hippocampus 1 month later when the dose was 2.5 mg/kg dose, but not at 1.25 mg/kg.\(^5\)\(^8\) Thus, for this multiple dosing regimen, 1.25 mg/kg could be taken as the NOAEL in the rhesus monkey.

In the rat, a single oral administration of 10 mg/kg did not affect brain serotonin levels and serotonin re-uptake site densities.\(^5\)\(^9\) However, Schmidt\(^6\)\(^0\) and Stone and co. workers\(^6\)\(^1\) found reduced brain serotonin in rats 1 or 2 weeks after the animals had been given a single subcutaneous injection of 10 mg/kg MDMA. A single intraperitoneal administration of 5 mg/kg MDMA did not reduce serotonin and 5-HIAA levels in the rat brain 7 days later, but a 10 mg/kg dose did.\(^6\)\(^2\) Intraperitoneal injections of 4 mg/kg once daily for 4 days did not reduce brain serotonin neuronal markers in the brain of the Dark Agouti rat (a strain of rats that is more sensitive to MDMA-induced neurotoxicity than other strains) 7 days later. However, injections twice a day for the same period of time did reduce these markers.\(^6\)\(^3\) Apparently, administration of 4–10 mg/kg MDMA causes serotoninergic deficits in rat brain depending on the experimental conditions. A reasonable NOAEL estimate in the rat would be 4–5 mg/kg if doses are separated by at least 1 day. This may be too short for man because of a slower elimination half-life of MDMA, and possibly slower recovery of neurones in man.

Applying allometric scaling factors to these data gives a predicted NOAEL for MDMA in man of 0.34 and 0.4–0.5 mg/kg using single-exposure squirrel monkey and rat data, respectively. The multiple dosing rhesus monkey data would yield a predicted NOAEL in man of 0.5 mg/kg. However, the corresponding rat data suggest that 0.4 mg/kg still could reduce serotonin neuronal markers in man. Thus, 0.4 mg/kg would appear to be a reasonable estimate of the NOAEL in man for single doses only. As the recreational dose of MDMA is 1–1.7 mg/kg (36,64), this results in a margin of safety of 0.24–0.4. This is roughly three times lower than for MBDB, suggesting that MDMA is more likely to cause neurotoxicity.

There are several points cautioning against taking these estimates as absolute figures and, therefore, the calculations presented above should be seen as illustrative for the margin of safety method only. First, only one kind of adverse effect (reduction of serotonin neuronal markers) was looked at in such a way that a NOAEL could be derived. To render a risk assessment valid, all kinds of toxic effects should be taken into account. In other words, a full toxicological investigation should be performed in order to identify acceptable safety margins. At present, toxicological data on MDMA and especially MBDB are so scarce that any risk assessment would be hazardous. Secondly, we extrapolated average responses in animals to man, disregarding intraspecies differences in suscepti-
bility for nerve terminal degeneration. Thirdly, the circumstances under which drugs are taken may affect the outcome. From animal experiments we know that hyperthermia increases the neurotoxicity of MDMA. Such factors were not taken into account in our calculations.

Acknowledgements
This study was supported by the European Monitoring Centre for Drugs and Drug Addiction.

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