

ACMD

Advisory Council on the Misuse of Drugs

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Rt Hon Theresa May MP, Home Secretary
Home Office
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28 November 2013

Dear Home Secretary,

In May 2013, the ACMD advised that a group of novel highly potent hallucinogens, the 'NBOMe' compounds, and some related analogue compounds, be subject to a temporary class drug order. You accepted this advice and a temporary class drug order came into force on 10 June 2013. These compounds were marketed as a legal product prior to this.

The ACMD has followed its initial assessment with a further consideration of the evidence available on the 'NBOMe' compounds in the context of the Misuse of Drugs Act (1971). I enclose this advice and generic definition with this letter.

An example of these materials, 25I-NBOMe, acts as a highly potent agonist for the human 5-HT_{2A} receptor. There is a high risk of overdose owing to the extremely high potency of these materials, even at microgram amounts of powder, and they are regarded as probable alternatives to LSD. There have been reported fatalities associated with the 'NBOMe' compounds, both in the UK and internationally. The ACMD is also aware that one of the NBOMe compounds has a legitimate use in PET scanners and autoradiographic studies.

The 'NBOMe' compounds are variants of phenethylamine materials which are controlled as class A substances under the Misuse of Drugs Act (1971). The 'NBOMe' modification of these compounds however renders them outside of the scope of these controls. The generic definition proposed in this report would bring these materials under the control of the Misuse of Drugs Act (1971).

The ACMD therefore recommends that the 'NBOMe' compounds covered by the proposed generic definition in Annex A, are controlled under the Misuse of Drugs Act (1971) as class A substances. They should be scheduled under Schedule I of the Misuse of Drugs Regulations (2001) as they have no known recognised medicinal use, however the following should be allowed for the legitimate use as a medical product in PET scanners, or in autoradiographic studies:

- [¹¹C]-25I-NBOMe (described by Ettrup *et al*, 2010,2013), and,
- the tritium labelled form of this compound (described by Nichols *et al*, 2008).

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Les Iversen'.

Professor Les Iversen

Cc: Norman Baker MP, Minister for Crime Prevention

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‘NBOMe’ compounds: A review of the evidence of use and harm

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Introduction

- 1.1. In early 2013, the ACMD became aware of a group of novel highly potent hallucinogens in the UK, the 'NBOMe' compounds. This paper reviews the evidence of misuse and harm in relation to the 'NBOMe' compounds, which has been considered by ACMD at meetings of the Novel Psychoactive Substances Committee in April 2013 and by the full Council in May and October 2013. A Temporary Class Drug Order (TCDO) for these substances and some analogues related to these compounds came into force on 10 June 2013.¹

2. Chemistry and pharmacology

- 2.1. The NBOMe materials are variants of the 2C-X series of psychoactive phenethylamines described by Shulgin (2000) in his book 'PIHKAL'. The 2C-X materials are 2,5-dimethoxyphenethylamines with a variety of substituents at the 4-position. The 2C-X materials are controlled under the Misuse of Drugs Act 1971 as Class A drugs. The NBOMe materials were first reported in 2003 by Ralph Heim at the Free University of Berlin (Heim, 2003). David Nichols of Purdue University further developed the 2C-X materials formed by adding a 2-methoxybenzyl (MeOB) onto the nitrogen (N) of the phenethylamine (hence presumably 'NBOMe') (Braden et al., (2006)). The full chemical name of 25I-NBOMe, for example, is 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine.
- 2.2. Nichols *et al.*, (2008) reported the synthesis of a high specific activity tritium-labelled form of 25I-NBOMe as a selective radioligand for mapping 5-HT_{2A} receptors in animal brain, and Ettrup *et al.*, (2010) described the radiosynthesis of a C¹¹-labelled form of this compound. Ettrup *et al.*, (2013) further reported a preclinical safety assessment of this compound as a potential tool for Positron Emission Tomography (PET) imaging of 5-HT_{2A} receptors in human brain, in rats and pigs. They concluded that an effective dose of the radiotracer was not associated with prohibitively high levels of radiation dosimetry. Furthermore, the dose of [C¹¹]-25I-NBOMe required for imaging studies was much lower than the doses associated with pharmacological effects in rodents (head twitch response). The authors concluded that [¹¹C]-25I-NBOMe could be administered safely to humans for use in PET scanning.

¹ Following agreement at the ACMD Council meeting on 16 May 2013

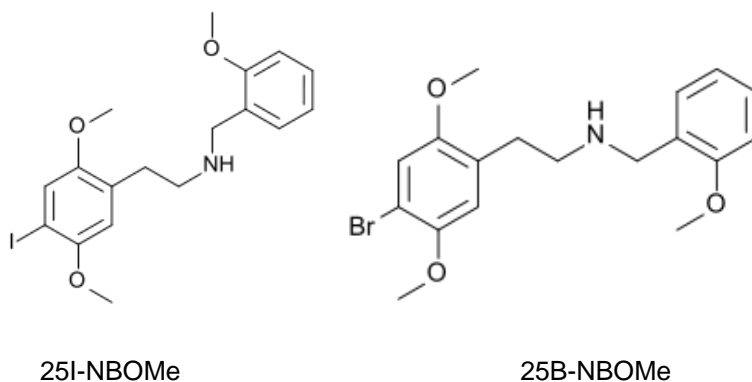


Figure 1. The structure of 25I-NBOMe and 25B-NBOMe

- 2.3. The addition of 2-methoxybenzyl significantly enhances the potency of the phenethylamines so, for example, while a dose of 2C-I is around 20 milligrams, a dose of the 'NBOMe' form ('25I-NBOMe') is less than one milligram (Blaazer *et al.*, 2008). The common dose is typically 50-100 µg. At these levels of potency, attempting to use powder or liquid dosage forms is dangerous, as there is a greater risk of overdose related to errors in user dose measurement. Prior to the laying of a TCDO in June 2013, some suppliers opted for selling it in the form of pre-loaded paper doses (blotters), similar to LSD 'tabs', so that users could take prepared dosage units, or as a spray.² The materials are hallucinogens of comparable potency to LSD, and so are probably regarded as alternatives to LSD. The 'NBOMe' compounds are reported to be inactivated if taken orally and so are usually taken by holding in the mouth (sub-lingual or buccal) or via the nasal membranes. Some Internet suppliers claim to offer the materials as a complex with hydroxypropyl-beta-cyclodextrin to improve their bioavailability.
- 2.4. The common and street names include: Bom-25; 2C-I-NBOMe; 25I-NBOMe; 25I; N-Bomb; and Smiley Paper.



Figure 2. A powder sample of 25I-NBOMe and pre-loaded paper doses on 'tabs'.

- 2.5. The hallucinogenic effects of LSD are thought to be due to its potent partial agonist action on 5-HT_{2A} receptors. Although LSD binds to several other 5-HT receptors, its affinity for 5-HT_{2A} sites appears crucial (Marek & Aghajanian, 1996; Nelson *et al.*, 1998; Egan *et al.*, 1998). 25I-NBOMe acts as a highly potent full agonist for the human 5-HT_{2A} receptor, of similar affinity to LSD (LSD Ki = 4.0 nM) (Nichols *et al.*, 2008). It is one of the only full agonists of the human 5-HT_{2A}

² (<http://www.chemsrus.com>)

receptor in existence (Braden *et al.*, 2006; Ettrup *et al.*, 2010; Nichols *et al.*, 2008; Silva *et al.*, 2011)

Table 1: 25I-NBOMe -Ki values – nM (Ettrup *et al.*, 2010)

5-HT _{2A}	2.2
5-HT _{2B}	2.3
5-HT _{2C}	7.0
5-HT ₆	58.0
5-HT _{1A}	85.0

3. Legislation

- 3.1. The Misuse of Drugs Act, Schedule 2 Part 1 (c) controls the following substances of the phenethylamine family as class A substances:

“any compound (not being methoxyphenamine or a compound for the time being specified in sub-paragraph (a) above) structurally derived from phenethylamine an *N*-alkylphenethylamine, α -methylphenethylamine, an *N*-alkyl- α -methylphenethylamine, α -ethylphenethylamine, or an *N*-alkyl- α -ethylphenethylamine by substitution in the ring to any extent with alkyl, alkoxy, alkylendioxy or halide substituents, whether or not further substituted in the ring by one or more other univalent substituents.”

- 3.2. The ‘NBOMe’ modification has the effect of making the materials outside the scope of the current UK generic controls on phenethylamines.

4. Use and prevalence

- 4.1. Data on the use of 25I-NBOMe is not included in the Crime Survey for England and Wales or other subpopulation surveys such as MixMag or *in-situ* club/festival surveys.
- 4.2. There was no evidence of significant use in recent self-report user surveys (Global Drug Survey, 2013 – aka Mix-Mag drug survey), although there is evidence from club outreach services that ‘NBOMe’ is a popular club drug and that it is mostly bought from the Internet.
- 4.3. The Serious Organised Crime Agency (SOCA)³ reported to the ACMD (May 16th, 2013) evidence that sizeable amounts of 25I-NBOMe had already arrived in the UK for distribution in blotter and powder format. This appeared to have arrived via a well-established link to producers of the drug in China, from where significant quantities of this and other NPS continue to be acquired in the UK. 25I-NBOMe is potentially a highly profitable drug, since a relatively small amount of powder can generate many doses at prices between £2-£4 (up to 20 million doses from 1kg). The substance may commonly be mistaken for LSD by sellers and users.

³ now the National Crime Agency

- 4.4. A SOCA quarterly report on seizure results (of 26th September 2013) reported the following number of samples taken:

Q1 of 2013 (January-March)- 10 samples;
Q2 of 2013 (April to June)- 10 samples.

5. Medical harms

- 5.1. Users report that 25I-NBOMe produces effects that can last between 6 and 10 hours, if taken sublingually. These self-reported, anecdotal user reports included the following effects: euphoria, mental/physical stimulation, feelings of love/empathy, a change in consciousness and unusual body sensations. Highly negative effects included confusion, shaking, nausea, insomnia, paranoia and unwanted feelings.
- 5.2. The UK Focal Point (February 28, 2013) reported the detection of the new psychoactive substance 25I-NBOMe linked to a series of 7 non-fatal intoxication cases in January 2013, and a detailed report was subsequently published (Hill *et al.*, 2013). The patients, all young adult males, presented to hospitals in the north east of England with toxicity after recreational drug use. Clinically observed features included tachycardia (n=7), hypertension (n=4), agitation and aggression (n=6), visual and auditory hallucinations (n=6), seizures (n=2), hyperpyrexia (n=3), clonus (n=2), elevated white blood cell count (n=2) and metabolic acidosis (n=3). Two patients required admission to intensive care; one patient had severe rhabdomyolysis leading to renal failure; and all of the cases had elevated creatine kinase to varying degrees. Routes of administration were insufflation (4), oral (1) and intravenous (1). LC-MS-MS analysis was performed at the Medical Toxicology Centre, Newcastle University, with 25I-NBOMe identified as the main active substance in the plasma and urine in all seven cases. One patient had intravenously injected a liquid form of the drug purchased from a dealer. The other six patients bought the drug from the Internet in the form of a powder inside capsules. Some users swallowed the capsules, whilst others broke them open and insufflated the powder.
- 5.3. The Home Office's 'drugs early warning system' (DEWS) described 9 reported cases (5 hospitalisations) associated with 25I-NBOMe usage between March and October 2013. Users generally expressed violence, agitation and hallucinogenic effects.
- 5.4. Northumbria Police reported a hospital case in December 2012 where the patient had binged on alcohol and other substances including 25I-NBOMe (a significant amount was found in the blood). The patient had impaired kidney function, needed sedation and had to be placed on a ventilator.
- 5.5. Surrey Police reported the death of an 18-year old man in February 2013, thought to be related to 25CI-NBOMe and this is awaiting confirmation.

- 5.6. Avon and Somerset Police have reported a total of 10 seizures of this product, all in the paper form containing several doses (identical to LSD). One fatality has been reported, where a 22-year old male drowned after taking 'NBOMe' along with other controlled drugs.
- 5.7. The national programme on substance associated deaths (npSAD) reported that 25I-NBOMe and 25C-NBOMe were identified in one death reported on the npSAD mortality database (September 2013).
International reports
- 5.8. In 2012, there were hospitalisations associated with 25I-NBOMe in the USA. These included one fully published case report (Rose *et al.*, 2013); three cases published in abstract form where analytical confirmation was available (Kelly *et al.*, 2012); and 11 further cases published in abstract form without analytical confirmation (Rose *et al.*, 2012). There have also been fatalities alleged to be linked to this material. There are Internet forum reports of an American 'chemist' who imported 2C-I from Europe and then converted it into the more potent 'NBOMe' form, before transferring it onto paper doses (apparently with fatal results). The drug is believed to have been responsible for several deaths. In June 2012, two teenagers in Grand Forks, North Dakota and East Grand Forks, Minnesota fatally overdosed on a substance that was allegedly 25I-NBOMe. A 21-year-old man from Little Rock, Arkansas also died of an apparent overdose in October 2012 after taking a liquid drop of the drug nasally at a music festival.
- 5.9. An 18-year old in Scottsdale, AZ died on January 25, 2013 after ingesting 25I-NBOMe sold as LSD. After a toxicology screen the Maricopa County Medical Examiner's Office ruled the cause of death to be acute 25I-NBOMe poisoning. No alcohol, prescription drugs or other illicit drugs were found by the post-mortem. It is also the suspected cause of death in another case in Scottsdale on April 29, 2013, also involving an 18-year old.
- 5.10. A similar material (25C-NBOMe) was recently encountered in New Zealand as a 'legal high', and was rapidly made illegal there. [<http://www.sciencemediacentre.co.nz/2012/03/13/legal-high-dime-not-so-legal/>].
- 5.11. 25I-NBOMe has been implicated in a number of deaths in South Australia. One man died in March 2012, after beating himself to death against objects including trees and poles, after consumption of 25I-NBOMe and related substances.
- 5.12. The Belgian National Focal Point reported in August 2013 that there had been three intoxications with 25I-NBOMe; two of which happened in a home drug party setting, where the drug blotters were found.
- 5.13. The Austrian National Focal Point issued an alert in April 2013 concerning the sale of 25I-NBOMe in the form of LSD blotters.

6. Social Harms

- 6.1. The limited evidence available to date indicates that the NBOMe compounds will carry the same risks of personal and social harm as LSD. Because of their extremely high potency there is a high risk of overdose – particularly when the compounds are handled in liquid or powder form.
- 6.2. Prevalence of NBOMe compounds is very low in surveys with young adults conducted in nightclubs and festivals (*personal correspondence with Professor Fiona Measham*). They do not seem to be a drug of choice; they are not particularly prevalent and there is no evidence that they are associated with criminal behaviour, either through violent or acquisitive crime.

7. Recommendation

- 7.1. The ACMD considers that, in the case of the compounds covered by the generic at Annex A, they are drugs that are being, or are likely to be, misused, and that misuse is having, or is capable of having, harmful effects. The ACMD recommends that the group of novel psychoactive substances covered by the generic at Annex A, and in particular those currently subject to a TCDO listed below, are controlled under the Misuse of Drugs Act, 1971 as Class A substances, and as Schedule 1 substances under the Misuse of Drugs Regulations, 2001 as they have no legitimate medical use.
 - 2-(2,5-Dimethoxy-4-methylphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine
 - 2-(4-Bromo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine
 - 2-(4-Iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine
 - 2-(4-Chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine
- 7.2. The ACMD also recommends that [¹¹C]-25I-NBOMe, described by Ettrup *et al.*, 2010, 2013), and the tritium labelled form of this compound described by Nichols *et al.*, 2008, be allowed for the legitimate medical product use in PET scanners, or in autoradiographic studies. The use of these compounds in research applications involves amounts of substance well below those required for a pharmacological response (Ettrup *et al.*, 2013).

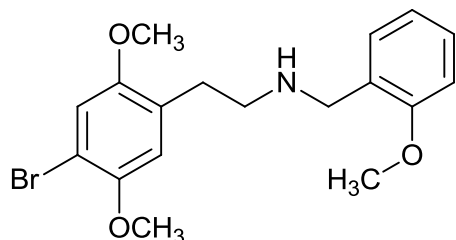
Annex A- Proposed generic definition

The following paragraph to be added to Schedule 2 Part 1 (Class A drugs)

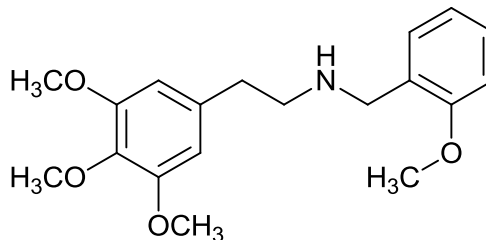
Any compound (not being benzyl(α -methyl-3,4-methylenedioxyphenethyl)amine) structurally derived from mescaline, 4-bromo-2,5-dimethoxy- α -methylphenethylamine, 2,5-dimethoxy- α ,4-dimethylphenethylamine, N-hydroxytenamphetamine, or a compound specified in paragraph 1(ba) or 1(c) above, by substitution on the nitrogen atom of the amino group with a benzyl substituent, whether or not substituted in the phenyl ring of the benzyl group to any extent.

Annex B- Examples of compounds covered by the proposed generic

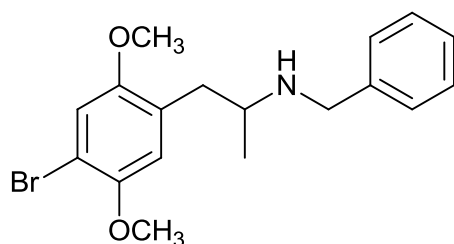
NBOMe compounds (Class A) of the ring substituted phenethylamines in Schedule 2 Part 1 paragraph 1(ba), paragraph 1(c) and four substances from paragraph 1(a)



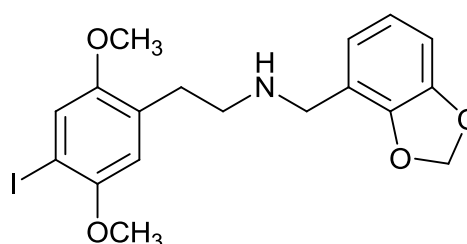
25B-NBOMe



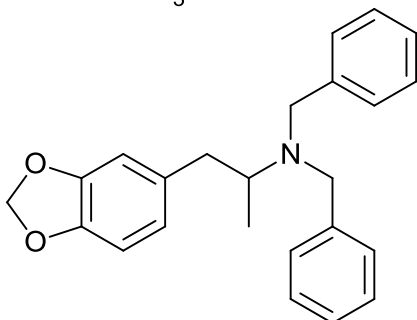
N-(2-methoxybenzyl) derivative of mescaline



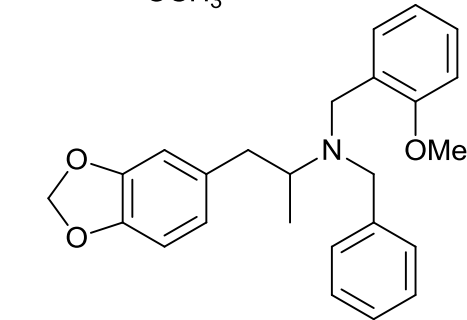
N-benzyl derivative of para 1(ba)
PIHKAL 103 -N-benzyl derivative



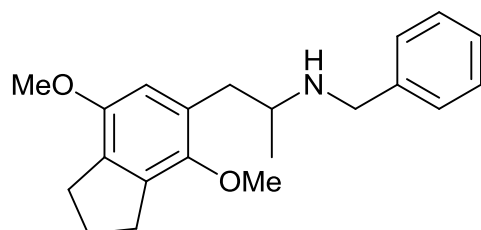
N-(2-methoxybenzyl) derivative of para 1(ba)
PIHKAL 103 -NBOMe derivative



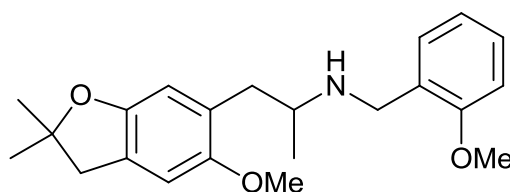
N-benzyl derivative of para 1(ba)
PIHKAL #82 -N-benzyl derivative



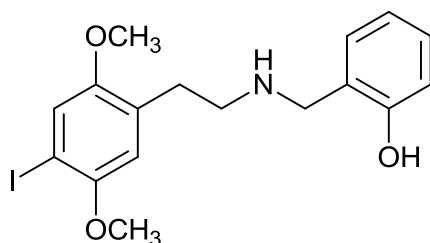
N-(2-methoxybenzyl) derivative of para 1(ba)
PIHKAL #80 -NBOMe derivative



N-benzyl derivative of para 1(ba)
PIHKAL #82 -N-benzyl derivative



N-(2-methoxybenzyl) derivative of para 1(ba)
PIHKAL #80 -NBOMe derivative



25I-NBOH

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