

25C-NBOMe
Critical Review Report
Agenda item 4.18

Expert Committee on Drug Dependence
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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of 25C-NBOMe18

Summary

25C-NBOMe is a substituted phenethylamine and derivative of 2C-C. It is a potent partial agonist of the serotonin 5-HT_{2A} receptor in particular and appears to have stimulant and particularly hallucinogenic effects. It has been associated with non-fatal intoxication and death, with seized material and use reported in many more. It has been reportedly sold as LSD or as a 'legal' alternative to LSD or "research chemical" usually via Internet websites. The variation in formulations and resultant dosage coupled with its potency results in health risks to the individual. There are not much data concerning the abuse or dependence potential of 25C-NBOMe.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not applicable

B. *Chemical Abstract Service (CAS) Registry Number*

1227608-02-7

C. *Other Names*

2C-C-NBOMe; 25C-NBOMe; 25C; 2CCNBOMe; 2C-C-NBOMe; NBOMe-2C-C; NBOMe-2CC;

2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine

2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethan-1-amine

4-chloro-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine

4-chloro-2,5-dimethoxy-N-(o-methoxybenzyl)phenethylamine

4-chloro-2,5-dimethoxy-N-[(2-methoxyphenyl)methyl]-benzeneethanamine

N-(2-methoxybenzyl)-2,5-dimethoxy-4-chlorophenethylamine

N-(2-methoxybenzyl)-4-chloro-2,5-dimethoxyphenethylamine

Cimbi-82 (¹¹C radiolabelled for PET scanning) - Center for Integrated Molecular Brain Imaging (CIMBI)

D. *Trade Names*

None

E. *Street Names*

C-Boom; 25C; legal acid; NBomb; NE-BOME; Pandora; Dime; NBOMe-2C-C, BOM 2-CC

The drug is most often listed on “research chemical” websites as 25C-NBOMe. 25C- refers to the 2,5-dimethoxy-4-chlorophenethylamine (2C-C) portion of the structure with NBOMe referring to the N-Benzoylmethoxy moiety (methoxy being OMe in chemical shorthand).

F. *Physical properties*

25C-NBOMe hydrochloride is a powder.

G. *WHO Review History*

25C-NBOMe was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO’s attention that 25C-NBOMe is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

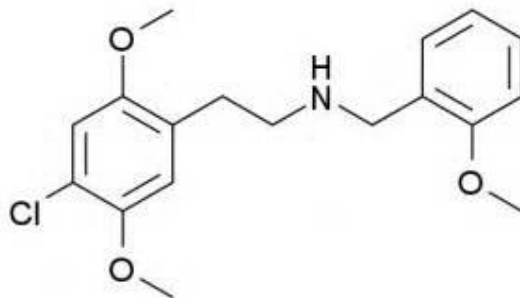
A. *Chemical Name*

IUPAC Name: 2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine

CA Index Name: Not applicable

B. *Chemical Structure*

Free base:



Molecular Formula: C₁₈H₂₂ClNO₃

Molecular Weight: Free base = 335.8

Melting point: not known

Boiling point: not known

Fusion point: not known

C. *Stereoisomers*

25C-NBOMe has no chiral centres and therefore no stereoisomers.

D. *Synthesis*

Although not specifically included in the thesis, it is conceivable that the synthesis of 25C-NBOMe would be through the same synthetic process first mentioned by Heim in a thesis at the Free University of Berlin (2003). It is a stepwise reductive alkylation where the reducing agent (NaBH₄) is added after the imine intermediate is formed first by the addition of 2-methoxybenzaldehyde to the starting (i.e. 2C-C) compound (Abdel-Magid *et al.* 1996). Various researchers have used this process to synthesise a variety of NBOMe structures for chemical testing, including 25C-NBOMe (Casale and Hays, 2012; Hansen *et al.*, 2014). Published methods typically produced the hydrochloride salt.

E. *Chemical description*

25C-NBOMe is a derivative of 2C-C (4-chloro-2,5-dimethoxyphenethylamine), a known synthetic derivative of phenethylamine with stimulant and hallucinogenic properties. 25C-NBOMe contains the 2C-C substructure, substituted with a 'N-(2-methoxy)benzyl' group.

Several NBOMe derivatives exist where the chlorine atom is exchanged for another halide element, hydrogen atom or organic functional group, i.e. iodine

(25I-NBOMe), bromine (25B-NBOMe), hydrogen atom (25H-NBOMe), -methyl (25DNBOMe), -ethyl (25E-NBOMe), -nitro (25N-NBOMe) or -isopropyl (25iP-NBOMe).

F. Chemical properties

See Section B and G.

G. Chemical identification

Given its chemically basic nature, the extraction of 25C-NBOMe is relatively straightforward as it is direct analysis of the compound itself (e.g. as a powder or in liquid form) by a number of techniques. However, as detailed elsewhere, in biological fluid, concentrations present after use may be very low and therefore require the application of very sensitive techniques (e.g. tandem mass-spectrometry). Detection methods such as gas chromatography with mass-spectrometry (GC-MS), high performance liquid chromatography with diode-array detection (HPLC-DAD) and/or mass-spectrometry (LC-MS) and accurate mass spectrometry have been published as part of case studies (Soh and Elliott 2013, Casale and Hays 2012, Zuba *et al.*, 2013, Poklis *et al.*, 2014). The detection outputs depend on the technique used but for 25C-NBOMe with LC-MS, the protonated molecular ion [M+H] of 336 m/z is observed with fragmentation resulting in a predominant 121 m/z ion of the N-(2-methoxy)-benzyl fragment as well as a 91 m/z fragment ion (Soh and Elliott 2013, Casale and Hays 2012, Zuba *et al.*, 2013, Poklis *et al.*, 2013). The underivatized GC-electron impact mass spectrum for 25C-NBOMe has ion peaks at (m/z) = 121 (base peak); 77, 91, 150, 186 and 304 (Zuba *et al.*, 2013). No presumptive test data (including Marquis field tests) exist. There is no known cross-reactivity with commercially-available urine immunoassay tests for the standard drugs of abuse.

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

4.1. Pharmacodynamics

Animal studies

Data from in vitro studies have shown that 25B-NBOMe has nanomolar affinity for the serotonin 5-HT_{2A} receptor and is a partial agonist, with less affinity for the 5-HT_{2C} receptor (Hansen *et al.*, 2014; Ettrup *et al.*, 2010 and 2011). As for 25B-NBOMe and 25I-NBOMe, the addition of the 2-methoxybenzyl group is likely to significantly enhance the affinity and potency of 25C-NBOMe compared to 2C-C (Blaazer *et al.*, 2008; Juncosa *et al.*, 2013). Stimulation of the 5-HT_{2A} receptors appears to be essential for the hallucinogenic effects of drugs such as LSD (Egan *et al.*; 1998, Marek & Aghajanian, 1996; González-Maeso *et al.*, 2007; Hanks & González-Maeso, 2013; Nelson *et al.*, 1998). Binding (K_i) at the rat 5-HT_{2A} receptor was reported to be 2.89±1.05 nM with activation (ED₅₀) of 2.31±0.11 nM and intrinsic activity of 88% (Ettrup *et al.*, 2011).

Human data

Although tested in animals, there are no reported human clinical trials with 25C-NBOMe in the scientific literature. However, Ettrup *et al.* (2011 suppl) reported National Institute of Mental Health's Psychoactive Drug Screening Program (PDSP) K_i determinations at neuroreceptors including 5-HT_{2A} receptors showing binding (K_i) of 0.9 nM against [³H]LSD and 1.6 nM against [³H]ketanserin. Separately, whilst 25C-NBOMe is considered to be not orally active, there are no current human data to confirm or refute this. This perception has seemingly affected the routes of administration of user products (Section 4.2).

Based on user reports (Erowid), the duration of effects of 25C-NBOMe (no information on dose) are described as being;

Total duration:	6-8 hours (sublingual/buccal)	4-8 hours (insufflated)
Onset:	0-15 minutes (sublingual/buccal)	0-5 minutes (insufflated)
Coming up:	30-90 minutes (sublingual/buccal)	15-30 minutes (insufflated)
Coming down:	1-4 hours (sublingual/buccal)	1-3 hours (insufflated)

4.2. Routes of administration and dosage

Reported routes of administration for 25C-NBOMe include sublingual (especially “blotter” paper), buccal, nasal (insufflation and absorption of liquid solutions), oral, injection (intravenous and intramuscular), rectal and smoking. Information from case reports and user websites suggest a range of doses are used that may depend on the route of administration. Example doses reported on the Erowid user website include: ‘830 µg, injected’; ‘500 µg, insufflated liquid’; ‘600 µg, buccal’; ‘350 µg, sublingual’; ‘1200 µg, sublingual’; ‘800 µg, oral’; ‘300 µg, sublingual’ (Erowid, see also: Blue Light Forum, Drug Forum).

Information from user websites suggest that 25C-NBOMe may be used on its own as well as in combination with other new psychoactive substances and/or controlled drugs (Erowid, Blue Light Forum, Drug Forum).

4.3. PharmacokineticsAnimal studies

There do not appear to be any published pharmacokinetic data for 25C-NBOMe in animals.

Human studies

Whilst there do not appear to be any published pharmacokinetic data for 25C-NBOMe in humans, Soh and Elliott (2013) reported the presumed detection of a desmethyl-metabolite and possible di-desmethyl- metabolite of 25C-NBOMe, respectively (through predicted O-demethylation) in casework biological fluid. This was also the case for 25I-NBOMe (Soh and Elliott, 2013, Stellpflug *et al.*, 2013).

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of 25C-NBOMe.

User reports from Erowid described the following subjective effects of self-reported 25C-NBOMe.

- | | |
|-------------------|---|
| “Positive” | <ul style="list-style-type: none"> Mental and physical stimulation Increase in associative & creative thinking Mood lift Open and closed eye visuals Increased awareness & appreciation of music Life-changing spiritual experiences Euphoria |
| “Neutral” | <ul style="list-style-type: none"> General change in consciousness Pupil dilation Difficulty focusing Unusual body sensations (facial flushing, chills, goosebumps, body energy) Change in perception of time Slight increase in heart rate Hot flushes and/or cold chills |
| “Negative” | <ul style="list-style-type: none"> Nausea Insomnia Paranoia, fear, and panic Unwanted and overwhelming feelings Unwanted life-changing spiritual experiences |

Adverse effects reported in a possible single non-fatal case report included; tachycardia, hypertension, seizures, hyperpyrexia (Nefcy *et al.* 2013). In a fatality reported by Soh and Elliott (2013), the deceased was found unresponsive and therefore no symptom information of was available (Elliott 2014).

6. Adverse reactions in humans

A possible single non-fatal intoxication and a death associated with 25C-NBOMe have been reported in the USA (Nefcy *et al.* 2013) and the United Kingdom (Soh and Elliott 2013), respectively.

For the **non-fatal case**, a 19 year old male US college student was found unconscious in the snow by campus police and was brought to an urban emergency room department with extreme agitation and confusion. An unmarked eyedropper with a small amount of clear liquid was found amongst his belongings, which he later said contained “2C-T-2 or 2C-T-7.” On exam he demonstrated sustained clonus and hyperreflexia without rigidity. Tachycardia, hypertension, mydriasis, flushing and diaphoresis were also noted. He was admitted to the Intensive Care Unit where rhabdomyolysis, hyperthermia and progressive dissociation developed over the next 36 hours. After treatment, he was

discharged home with complete resolution of his symptoms. Analysis of the eyedropper contents revealed “two variants of 2C-NBOMe” (but the exact identification was not stated) and an unidentified derivative of phencyclidine (PCP).

For the UK **fatal case**, in February 2013, a 18 year old male had been to a “rave” where he purchased two vials of liquid (believed to be 2C-I). He was thought to have nasally inhaled both (at some point). After the event he returned to a residence where he was found unresponsive in the morning and was pronounced dead. Analysis of vials found at the property detected 25C-NBOMe (with a trace amount of 25I-NBOMe). No further case information was available. Analysis of a post-mortem blood and urine specimen detected cannabinoids and 25C-NBOMe (Soh and Elliott 2013, Elliott 2014). No 2C-I or other NBOMes were detected. The concentrations of 25C-NBOMe in the blood and urine were determined to be less than 6.25 ng/mL, the limit of detection of the assay (Elliott 2014).

7. Dependence potential

No studies have examined the dependence potential of 25C-NBOMe *in vitro*, in animals or in humans.

8. Abuse potential

No studies have examined the abuse potential of 25C-NBOMe *in vitro*, in animals or in humans.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

25C-NBOMe has no recorded therapeutic applications or medical use. The use of radio-labelled 25C-NBOMe in medical research is discussed elsewhere.

10. Listing on the WHO Model List of Essential Medicines

25C-NBOMe is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

25C-NBOMe has never been marketed as a medicine.

12. Industrial use

25C-NBOMe has no industrial use.

13. Non-medical use, abuse and dependence

25C-NBOMe use and/or seized material has been reported in Croatia, Denmark, Finland, France, Germany, Hungary, Italy, Norway, Slovenia, Sweden, Turkey, the United Kingdom and the USA.

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Lawn *et al* undertook a study to examine the characteristics of users of 25B-NBOMe, 25C-NBOMe and 25I-NBOMe through the Global Drugs Survey (Lawn *et al.*, 2014). A total of 22,289 responses were collected in late 2012. One-third (n = 7,360; 33.9%) of respondents were from the UK, 7,784 (35.9%) were from Australia, 3,756 (17.3%) were from the USA, 2,164 (10.0%) were from the rest of Europe, and 618 (2.9%) were from Canada. Most (68.6%) respondents were male and the mean age was 31.4 years (SD = 12.4; range 16 – 100). 2.6% of respondents (n = 582) reported having ever tried one of the three NBOMe drugs and that at 2.0%, 25I-NBOMe was the most popular (n = 442) followed by 25B-NBOMe (n = 267; 1.2%) and 25C-NBOMe (n = 65; 0.8%). Almost all (93.5%) respondents whose last new drug tried was a NBOMe drug and 81.2% of this group administered the drug orally or sublingually/buccally. Subjective effects were similar to comparison serotonergic hallucinogens, though higher 'negative effects while high' and greater 'value for money' were reported. The most common (41.7%) drug source was via a website.

Information from seizures, collected samples and user websites suggest that 25C-NBOMe has been commonly sold as a 'legal' replacement for LSD or sold as LSD directly on the illicit drug market. In the latter case users may be unaware that they are using 25C-NBOMe. Nevertheless, it also appears to be associated with the purchase of "research chemicals" or equivalent products via the Internet as well clearly stated to be 25C-NBOMe "tabs". Instances of misuse, abuse and dependence would be limited to such individuals rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs. However, analysis of various products have shown that the composition can differ (including between that claimed by the retailer) and the user is unlikely to be aware of the exact dose or compound being ingested (by whatever route) which presents an inherent risk to the individual.

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances

15. Licit production, consumption and international trade

Refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

Refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

Not applicable in relation to affecting impact of medical use.

18. Current and past national controls

25C-NBOMe is currently controlled under drug control legislation in Denmark, Hungary, Israel, Lithuania, New Zealand, Portugal, Romania, Russia, Slovenia, Sweden and areas of Australia (Queensland and New South Wales). Furthermore it is party to a temporary class order in the United Kingdom (from June 2013 to be reviewed in June 2014) and under temporary Schedule I control in the USA (November 2013).

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Researchers have used radiolabelled 25C-NBOMe as a tool to study the serotonergic system in the brain (Ettrup *et al.*, 2010 and 2011) as part of work that ultimately aims to further the understanding of the pathogenesis of human disease in which the serotonergic system may play a role. This includes research into its potential use as a tracer in Positron Emission Tomography (PET) imaging studies (Ettrup *et al.*, 2010 and 2011).

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Background information and evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for temporary scheduling.

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Annex 1

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of 25C-NBOMe

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 64 Member States answered the questionnaire for **25C NBOMe**. Of these only 21 respondents (AMR 4, EUR 14, WPR 3) had information on this substance.

LEGITIMATE USE

None of the respondents reported that 25C NBOMe was currently authorized or in the process of being authorized/registered as a medical product in their country. Four respondents stated that this substance was used in medical and scientific research and as reference standards. There was no use stated in animal/veterinary care.

HARMFUL USE

Nineteen responses confirmed recreational/harmful use of 25C NBOMe; 12 stated that the common route of administration was oral with 3 stating this was by oral, inhaling/sniffing. As for the source for such use, 13 responded only via trafficking and one each via diversion plus trafficking and via clandestine manufacturing. Two reported the common formulations available as powder, six as powder and liquid, one as powder and tablet and one as tablet forms. Eight respondents also mentioned that 25C NBOMe was used on blotter paper. On the populations using the substance, two stated use by the general population and in clubs and 6 only in clubs and 3 only among general population. In general population, adolescents and young adults are specially mentioned. Six respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by 25C NBOMe. Two respondents reported deaths (four by one during 2013 -2013 and several by the other) related to the use of 25C NBOMe as well as emergency room admissions (adverse events include violent and erratic behavior, dizziness, head ache, extreme agitation etc). 25 I and 25C NBOMes were identified in one death in 2013. Harm similar to LSD is mentioned. (See also information provided for 25 B and I NBOME – these may have similar effects).

CONTROL

Of those with information on this substance, 15 reported that 25C NBOMe was controlled under legislation that was intended to regulate its availability; eight under “controlled substance act”, three under “medicines law”, two “temporary ban”, one “analogue legislation” and one under “other” laws. Three respondents stated that there were problems with the implementation of this legislation. On Illicit activities, five respondents reported processing into the consumer product, 13 reported trafficking, 3 diversion and 13 an internet market.

Details on seizures are presented below.

	Total numbers reported 2011 (number of respondents)	Total numbers reported 2012 (number of respondents)
Total number of seizures	1 (1)	98 (7)
Total quantity seized (kg)	No data	0.66 (3)
Total quantity seized (other)	504 (1, do not specify what)	745blotters (4)

IMPACT OF SCHEDULING

All respondents reported that if 25C NBOMe was placed under international control, they would have the laboratory capacity to identify the substance. There is no reported medical use for this substance.