25I-NBOMe

Critical Review Report

Agenda item 4.19

Expert Committee on Drug Dependence

Thirty-sixth Meeting

Geneva, 16-20 June 2014

Acknowledgments

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Contents

Summary

25I-NBOMe is a substituted phenethylamine and derivative of 2C-I. It is a potent full agonist of the serotonin 5-HT_{2A} receptor in particular and appears to have stimulant and particularly hallucinogenic effects. It has been associated with numerous non-fatal intoxications and some deaths, with seized material and use reported in many countries. 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 no data concerning the abuse or dependence potential of 25I-NBOMe.

1. Substance identification

A. ***International Nonproprietary Name (INN)***

Not applicable

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

Free base: 919797-19-6

Hydrochloride salt: 1043868-97-8

^{11}C radiolabelled base – ^{11}C on the benzyl methoxy carbon: 1248338-50-2

^{11}C radiolabelled base – ^{11}C on the phenyl 2-methoxy carbon: 1404305-56-1

^{3}H radiolabelled base: 1043869-41-5

C. ***Other Names***

2C-I-NBOMe; 25I-NBOMe; 25I; 2CINBOMe; 2C-I-NBOMe; NBOMe-2C-I; NBOMe-2CI;

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

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

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

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

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

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

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

Cimbi-5 (^{11}C radiolabelled for PET scanning) - Center for Integrated Molecular Brain Imaging (CIMBI)

D. ***Trade Names***

None

E. ***Street Names***

Solaris; 25I; Dots; legal acid; NBomb; NE-BOME; Smiles; INBMeO; BOM-CI; Hoffman; N-boom.

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

F. ***Physical properties***

25I-NBOMe hydrochloride is a powder.

G. *WHO Review History*

25I-NBOMe was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that 25I-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.

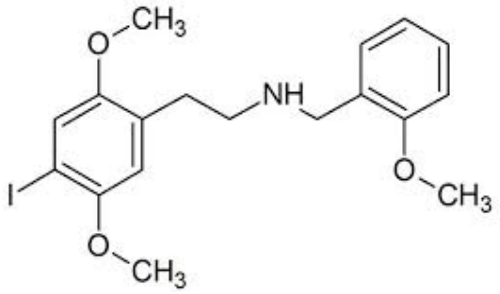
2. Chemistry

A. Chemical Name

IUPAC Name: 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine
CA Index Name: Not applicable

B. Chemical Structure

Free base:



Molecular Formula:	$C_{18}H_{22}INO_3$
Molecular Weight:	Free base = 427.2767
Melting point:	166°C (HCl salt) – Heim (2003)
Boiling point:	not known
Fusion point:	not known

C. Stereoisomers

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

D. Synthesis

The synthesis of 25I-NBOMe was first mentioned by Heim in a thesis at the Free University of Berlin (2003). It is a stepwise reductive alkylation where the reducing agent ($NaBH_4$) is added after the imine intermediate is formed first by the addition of 2-methoxybenzaldehyde to the starting 2C-I compound (Abdel-Magid *et al.* 1996). Various researchers have used this process to synthesise a variety of NBOMe structures for chemical testing, including 25I-NBOMe (Casale and Hays, 2012; Hansen *et al*., 2014). The free base product is a colourless oil. Published methods typically produced the hydrochloride salt.

E. Chemical description

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

Several NBOMe derivatives exist where the iodine atom is exchanged for another halide element, hydrogen atom or organic functional group, i.e. bromine (25B-NBOMe), chlorine (25C-NBOMe), hydrogen atom (25H-NBOMe), -methyl (25DNBOMe), -ethyl (25E-NBOMe), -nitro (25N-NBOMe) or –isopropyl (25iP-NBOMe).

These compounds are informally called the 'NBOMes'. This name comes from the '**N**-**b**enzylmethoxy' substituent (-methoxy being written in chemical shorthand as '**OMe**'). As of 12 December 2013, ten '-NBOMe' compounds have been notified to the EU early warning system and it is important to note that –NBOMe compounds can be derived from all '2C' phenethylamines. Furthermore, two simple variants of 25I-NBOMe are possible by moving the methoxy group, found in position -2 on the benzyl moiety, to position -3 or -4. Furthermore, many other chemical variants are possible by changing the substitution pattern on the benzyl moiety to produce substances, the effects of which may or may not be similar to 25I-NBOMe. (EMCDDA–Europol Joint Report on a new psychoactive substance: 25I-NBOMe (4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine; EMCDDA-Europol, Lisbon, January 2014).

F. Chemical properties

See Section B and G.

G. Chemical identification

Given its chemically basic nature, the extraction of 25I-NBOMe is relatively straightforward as 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 2014, Gillings 2009, Casale and Hays 2012, Rose *et al*., 2013, Hill *et al*., 2013, Stellpflug *et al*., 2013, Poklis *et al*., 2013, Walterscheid *et al.* 2014). The detection outputs depend on the technique used but for 25I-NBOMe with LC-MS, the pronated molecular ion [M+H] of 428 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 2014; Casale and Hays 2012; Rose *et al*., 2013, Hill *et al*., 2013, Stellpflug *et al*., 2013, Poklis *et al*., 2013, 2014, Walterscheid *et al.* 2014). 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 25I-NBOMe has nanomolar affinity for the serotonin 5-HT_{2A} receptor and is a full agonist (Braden *et al*, 2006; Ettrup *et al*., 2010; Ettrup *et al*., 2011; Nichols *et al*., 2008), with less affinity for the 5-HT_{2C} receptor (Hansen *et al.*, 2014). The addition of the 2-methoxybenzyl group significantly enhances the affinity and potency of 25I-NBOMe (Braden *et al*, 2006) compared to 2C-I (Blaazer *et al*., 2008). 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 & Aghaajanian, 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 1.49±0.35 nM with activation (ED_{50}) of 1.02±0.08 nM and intrinsic activity of 91% (Ettrup *et al*., 2011).

Given the fact that 25I-NBOMe is a potent full agonist for the 5-HT_{2A} receptor and there have been reports of its hallucinogenic effects when used as a recreational drug, Halberstadt and Geyer (2013) studied the effect of 25I-NBOMe on the head twitch behavioural response (HTR) in mice which is used as a surrogate marker of the hallucinogenic effect of 5-HT_{2A} receptor activation in humans (Hanks & González-Maeso, 2013). The study found that 25I-NBOMe induces HTR in mice in a dose dependent manner, with a dose of 0.01 mg/kg s.c. inducing significant HTR compared to controls. HTR was dose-dependently antagonised by pre-treatment of the mice with the 5-HT_{2A} receptor antagonist M100,907 suggesting that the HTR induced by 25I-NBOMe is mediated through 5-HT_{2A} receptor activation.

Separately, 25I-NBOMe was used in a psilocybin experiment in mice to study neurogenesis and the extinction of trace fear conditioning (Catlow *et al.* 2013). Injections of 25I-NBMeO (0.1, 0.3 and 1 mg/kg) or of the antagonist ketanserin resulted in a significant decrease in the number of surviving BrdU+ cells and BrdU/NeuN+ neurons in hippocampus compared to saline injections and unlike the psilocybin injections, low doses of 25I-NBMeO did not produce a trend toward increased neurogenesis.

Human data

Although tested in animals, there are no reported human clinical trials with 25I-NBOMe in the scientific literature. However, Braden *et al.* (2006) reported, using human embryonic kidney (HEK) 293 cells expressing wild-type human 5-HT_{2A} receptors, binding (K_i) of 0.044±0.006 nM with activation (EC_{50}) of 0.44±0.07 nM and intrinsic activity of 81 %. Separately, whilst 25I-NBOMe is considered to be not orally active, there is 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 25I-NBOMe (no information on dose) are described as being;

Total duration:	6-10 hours (sublingual/buccal)	4-6 hours (insufflated)
Onset:	15-120 minutes (sublingual/buccal)	5-10 minutes (insufflated)
Coming up:	30-120 minutes (sublingual/buccal)	10-30 minutes (insufflated)
Plateau:	120-240 minutes (sublingual/buccal)	60-120 minutes (insufflated)
Coming down:	60-240 minutes (sublingual/buccal)	120-180 minutes (insufflated)
After effects:	1-7 days (sublingual/buccal)	1-7 days (insufflated)

4.2. Routes of administration and dosage

Reported routes of administration for 25I-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/series 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: '750 µg, sublingual'; '3750 µg, sublingual'; '1000 µg, sublingual'; '1mg, buccal'; '1 blotter hit, sublingual/buccal'; '1000 µg, insufflated'; '500-1000 µg, smoked' (Erowid). Further examples are provided in Section 6 (see also: Blue Light Forum, Drug Forum, Hill *et al*., 2013, Stellpflug *et al*., 2013).

Information from user websites suggest that 25I-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). This is supported by reported non-fatal intoxications and deaths following analysis of biological samples (Section 6).

4.3. Pharmacokinetics

Animal studies

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

Human studies

Whilst there do not appear to be any published pharmacokinetic data for 25I-NBOMe in humans, Stellpflug *et al* (2013) reported the presumed detection of a desmethyl-metabolite of 25I-NBOMe (through predicted O-demethylation) in casework biological fluid and Soh and Elliott (2014) reported the presumed detection of a desmethyl-metabolite of 25C-NBOMe. Although 25H-NBOMe was also detected by both author groups, this may not be through metabolism (due to the unclear existence of a metabolic pathway that would remove the iodine) and could be due to 25H-NBOMe being present as a contaminant in the product consumed (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 25I-NBOMe.

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

"Positive"
Strong open and closed eye visuals, including trails, colour shifts, brightening, etc.
Mood lift
Euphoria
Mental and physical stimulation
Increase in associative & creative thinking
Increased awareness & appreciation of music
Life-changing spiritual experiences
Erotic, sexual thoughts and sensations
Feelings of love and empathy

"Neutral"
General change in consciousness
Pupil dilation
Difficulty focusing
Unusual body sensations (facial flushing, chills, goosebumps, body energy)
Change in perception of time, time dilation
Slight increase in heart rate
Yawning, especially when coming up
Does not suppress appetite

"Negative"
Confusion
Looping
Scrambled communication
Nausea
Insomnia
Looping, recursive, out of control thinking
Paranoia, fear, and panic
Unwanted and overwhelming feelings
Unwanted life-changing spiritual experiences
Vasoconstriction, peripheral numbness, swelling of feet, hands, face

Clinical admissions and case reports have described various toxic effects including; tachycardia, hypertension, confusion, agitation, aggression, visual and auditory hallucinations, seizures, hyperpyrexia, clonus, metabolic acidosis, rhabdomyolysis and acute kidney injury (Kelly et al. 2012, Rose et al. 2012, 2013, Hill et al. 2013, Stellpflug et al 2013). The clinical hospitalizations reported by Hill et al (2013) also reported elevated creatine kinase in all seven cases with elevated white cell count in two.

6. Adverse reactions in humans

Non-fatal intoxications and deaths associated with 25I-NBOMe have been reported by Australia (at least 2 deaths), Belgium (3 non-fatal, 1 unconfirmed death), Poland (4 non-fatal, 1 unconfirmed death), Sweden (18 non-fatal), the United Kingdom (7 non-fatal, 1 death) and the USA (19 non-fatal, 11 combined NBOMe deaths, 5 25I-NBOMe deaths). Many but not all of these cases have been analytically confirmed.

Non-fatal cases

Belgium

Belgium reported three non-fatal intoxications to the EMCDDA which occurred in August 2013. The cases were linked as the subjects had all been at the same party. All cases had analytical confirmation with 25I-NBOMe detected in urine and negative results for other drugs. 25I-NBOMe was not quantified. The patients were admitted to the hospital, having consumed 'synthetic LSD' and symptoms included lowered consciousness, insufficient breathing, mydriasis, tachycardia, hypertension and one patient had 'lessened strength in four extremities'. Treatment included sedation, intubation and ventilation. The outcome is known for one patient whose symptoms disappeared after being under observation for a couple of hours. The patient reported having used 25I-NBOMe in the past.

Poland

Poland reported four linked non-fatal intoxication cases to the EMCDDA which occurred in August 2013. None of the cases were confirmed analytically. One of the patients reported they all had used 25I-NBOMe.

Sweden

Sweden reported 18 non-fatal intoxications to the EMCDDA which occurred between June 2012 and July 2013. Five of these cases were analytically confirmed. Symptoms reported included mydriasis, anxiety, agitation, hallucinations, psychotic symptoms, tachycardia and hyperthermia. The routes of administration noted were oral, nasal and by injection.

United Kingdom

Hill *et al.,* (2013) reported seven cases where 25I-NBOMe was detected and which occurred over the course of one week. The first case involved a 29-year old male who had purchased the drug from a 'dealer' in liquid form, labelled as '25I-NBOMe'. This person injected 3 ml of the liquid of unknown concentration intravenously. Symptoms included; agitation, aggression, seizures, self-harming behaviour associated with tachycardia, hypertension, tachypnea, oxygen desaturation, pyrexia and rhabdomyolysis. The patient also developed anuria with a subsequent acute kidney injury. A computed tomography (CT) scan revealed mild cerebral oedema but no other intracranial pathology. Treatment consisted of initial resuscitation with intubation, ventilation, intravenous sedation, antibiotics and fluids. Ongoing jerking seizure-like movements were noted and managed with atracurium infusion. Large doses of multi-modal sedation were administered during stabilisation. On day 18 of treatment a percutaneous tracheostomy was performed. The patient was discharged from intensive care on day 38, and discharged from hospital on day 43. In the other six cases, 25I-NBOMe had been taken at a house party after it had been purchased from the Internet.

The 25I-NBOMe was in the form of powder contained in purple capsules, labelled as '2C-B'. The six cases were analytically confirmed either in plasma alone or in urine and plasma. Amphetamine and methamphetamine were detected together with 25I-NBOMe in all six patients. 2C-I was also detected in the available urine samples (four of the seven cases) and it was suggested that 2C-I may be a metabolite of 25I-NBOMe but could equally be present as a product of synthesis. In three cases the capsules were swallowed and in the other three cases, the powder from the capsule was nasally insufflated. The quantities consumed were inexact, but were reported to range from one capsule (three cases) to 'small amount' or '~0.1 g' of powder. The patients typically presented with agitation, aggressive behaviour, palpitations, visual and auditory hallucinations, mydriasis, pyrexia, but the symptomatology varied slightly between patients. One of these patients suffered severe toxicity, which required hospitalisation for 5 days. He was treated with intravenous diazepam for agitation, was intubated and received pressure-controlled ventilation, anaesthesia with infusions of propofol, midazolam and atracurium. The remaining five patients were discharged from hospital on the same day as admission or within 15 hours and were treated with benzodiazepines (information available for three cases). Regular use of other illicit drugs was reported for three of the cases: one was a regular user of cocaine, cannabis and "Ecstasy" and had previously used LSD; another had a history of regular amphetamine and "Ecstasy" use; and, the third was a regular user of cannabis. One patient suffered from asthma and one patient was being treated with fluoxetine for depression.

USA

Kelly *et al.,* (2012) reported that four males between the ages of 18 and 19 simultaneously presented to the emergency department (ED) after recreational exposure to 25I-NBOMe. They purchased the drug from a dealer who obtained it through the internet. The substance was either snorted or ingested orally. Upon arrival, all patients were tachycardic and displayed varying levels of psychomotor agitation. None were capable of providing a clear history. Three patients experienced prolonged seizure activity which required pharmacologic therapy, intubation, and mechanical ventilation. Patient D developed rhabdomyolysis and renal failure requiring haemodialysis.

	Heart Rate	BP	Seizures?	Intubated?	Urine 25I (ng/mL)	Urine Other drugs
Patient A	122	121/56	no	no	2	caffeine
Patient B	108	140/60	yes	yes	N/A	N/A
Patient C	153	148/49	yes	yes	36	caffeine
Patient D	184	107/82	yes	yes	28	caffeine, nicotine

Rose *et al.,* (2012) reported ten patients with an average age of 17 years (range 14 – 20 years) presented to local emergency departments after ingestion and/or insufflation of a drug referred to as " 25-I " . Six of the ten reported 25-I alone; other substances admitted to by the other four included ethanol, 2-CE, THC and ketamine. Most common effects included tachycardia (90%), hypertension (70%), agitation (60%) and hallucinations (50%). The average heart rate was 123 beats per minute (range: 78 – mid 150s). Two patients were found in status epilepticus and another was found unresponsive. One of the patients who had a seizure was found to have multiple, discrete intraparenchymal haemorrhages and acute kidney injury. Hyperthermia was not documented in any case. Sixty percent of patients were admitted to the ICU, two were treated in the ED and released, and one each was admitted to psychiatry or managed in

a clinical decision unit and subsequently discharged. Three patients required emergent intubation, and all admitted patients were given intravenous benzodiazepines for sedation. All patients were discharged in good condition once symptoms resolved.

Subsequently, Rose *et al.*, (2013) reported the case of an 18-year-old male who presented to the ED with severe agitation and hallucinations after jumping out of a moving car. He was tachycardiac (150 – 160 bpm) and hypertensive (150 – 170 mm Hg systolic and 110 mg Hg diastolic), and required physical restraints and treatment with intravenous lorazepam administration. His symptoms gradually improved and vital signs returned to normal over 48 hours, though he continued to have episodes of aggressiveness. A 25I-NBOMe concentration of 0.76 ng/mL was in a serum sample obtained during ED evaluation and treatment.

Stellpflug *et al.*, (2013) reported the case of an 18 year old female admitted to an ED after a reported grand mal seizure following self-reported sublingual use of 25I-NBOMe. The clinical features reported included tachycardia, hypertension, agitation and confusion. She improved with intravenously administered fluids and benzodiazepines and was discharged 7 hours post-ingestion. 25I-NBOMe was found at a concentration of 7.5 ng/mL in the urine as well as desmethyl-25I-NBOMe (presumptive), 25H-NBOMe (0.9 ng/mL) and 2C-I (1.8 ng/mL).

Poklis *et al.*, (2014) reported the presence of 25I-NBOMe in three emergency room patients. The patients presented with signs and symptoms of drug intoxication including: tachycardia, hypertension, severe agitation and seizures. In one case, only 25I-NBOMe was detected at 0.1 ng/mL (matrix not stated), with another case involving 25I-NBOMe (2.3 ng/mL) and 25C-NBOMe, with the final case involving 25I-NBOMe (1.2 ng/mL) and 25H-NBOMe.

Fatal cases

Australia

25I-NBOMe has been implicated in a number of deaths in 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 (including possibly 25B-NBOMe) (Telegraph Australia 2012). In June 2013, a 17 year old male died in a fall from a balcony after taking something sold to him as LSD, but the tablet taken was reported by the Police to be 25I-NBOMe (The Australian 2013, Telegraph Australia 2013, Caldicott *et al*., 2013). No further information or biological fluid analytical confirmation available for any of the cases.

Belgium

One death was reported to the EMCDDA which occurred in October 2013. The cause of death was not been reported. The person died after consuming a blotter at a party that was believed to contain LSD; no LSD was detected in the toxicological analyses. Analytical confirmatory findings for 25I-NBOMe have not been reported.

Poland

One death was reported to the EMCDDA which occurred in August 2013. The death was linked with the four non-fatal intoxications reported above. As noted, one of the four patients who received treatment reported they all had used 25I-NBOMe. The cause of death has not been reported and no analytical confirmation is available.

United Kingdom

A death due to drowning occurred in May 2013. 25I-NBOMe was found following analysis of the post-mortem femoral blood of the deceased as well as amphetamine, ketamine, lidocaine, 5-MeO-DiPT, DOI, 25C-NBOMe and 2C-I (Soh and Elliott, 2014). Information had indicated that the deceased had possible access to 25I-NBOMe, 2C-E and possibly 25C-NBOMe and 2C-B.

USA

The Drug Enforcement Agency (DEA) obtained medical examiner and post-mortem toxicology reports from various states implicating some combination of 25I-NBOMe, 25C-NBOMe and 25B-NBOMe in the death of 14 individuals. The average age of these individuals was 20 years (range 15 to 29 years). The circumstances surrounding the deaths included acute toxicity (11 cases), or unpredictable, violent behaviour due to 25I-NBOMe toxicity ultimately leading to death (3 cases). Within this series, in June 2012 two teenagers fatally overdosed on a substance that was allegedly 25I-NBOMe and a 21-year-old man died of an apparent overdose in October 2012 after taking a liquid drop of 25I-NBOMe nasally at a music festival. Furthermore, an 18-year old died in January 2013 after ingesting 25I-NBOMe sold as LSD. After a toxicology screen the 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.

Walterscheid *et al.*, (2014) reported 2 deaths due to 25I-NBOMe, where the decedents were attending ‘‘rave’’ parties before the terminal events. The first case involved a 21-year-old male driver who had admitted taking ‘‘acid’’ to his passenger. A sudden surge of violent behaviour caused him to pull over and destroy the interior of the car, and he then became unresponsive. The post-mortem examination was unremarkable internally despite numerous external superficial injuries consistent with physical aggression. The second case involved a 15-year-old female who was socializing outside a rave party, became ill, and rapidly deteriorated as friends transported her to the hospital. The post-mortem assessment showed external contusions but internal injuries were superficial. Comprehensive toxicological screens in both cases exhibited evidence of cannabis and 25I-NBOMe use.

7. Dependence potential

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

8. Abuse potential

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

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

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

10. Listing on the WHO Model List of Essential Medicines

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

11. Marketing authorizations (as a medicine)

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

12. Industrial use

25I-NBOMe has no industrial use.

13. Non-medical use, abuse and dependence

25I-NBOMe use and/or seized material has been reported in Austria, Australia, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom and the USA.
Briefly, information from the Member States as well as from case reports/series suggests that 25I-NBOMe may be used in a range of settings, including the home environment (where an individual is on their own or in the company of others) and recreational settings. In the latter case this includes informal settings (such as 'house parties') as well organised events (such as 'techno' music events).

The recent report on the 'NBOMe' compounds by the Advisory Council on the Misuse of Drugs in the United Kingdom noted that 'evidence from club outreach services that 'NBOMe' is a popular club drug and that it is mostly bought from the Internet' (Advisory Council on the Misuse of Drugs, 2013). EMCDDA–Europol Joint Report on a new psychoactive substance: 25I-NBOMe EMCDDA-Europol, Lisbon, January 2014.

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 25I-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 25I-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 25I-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

25I-NBOMe is currently controlled under drug control legislation in Brazil, Denmark, Israel, Latvia, Slovenia, Norway, Russia, 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). In Austria, Hungary, Poland and Romania, 25I-NBOMe is subject to control measures under legislation covering unauthorised supply of defined or qualifying new psychoactive substances. In Finland and the Netherlands, 25I-NBOMe is subject to control measures under medicines legislation.
Sixteen Member States (Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Ireland, Italy, Lithuania, Luxembourg, Malta, Portugal, and Slovakia) and Turkey have reported that 25I-NBOMe is not subject to control measures at the national level.

No information was provided regarding the control status of 25I-NBOMe in Spain. 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 25I-NBOMe as a tool to study the serotonergic system in the brain (Ettrup *et al.*, 2010; Ettrup *et al.*, 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; Ettrup *et al*., 2011).

References

Abdel-Magid AF, Carson KG, Harris BD, Maryanoff CA, Shah RD (1996). Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures. J Org Chem 61: 3849-3862.

Aghaajanian GK and Marek GJ (1999). Serotonin and hallucinogens. Neuropyschopharmacology 21: 16S-23S.

Blaazer AR, Smid P, Kruse CG (2008). Structure-activity relationships of phenylalkylamines as agonist ligands for 5-HT($_{2A}$) receptors. ChemMedChem 3: 1299–1309.

Bluelight Forum: http://www.bluelight.org/vb/threads/551797-The-Big-amp-Dandy-25I-NBOMe-Thread.

Braden MR, Parrish JC, Naylor JC, Nichols DE (2006). Molecular interaction of serotonin 5-HT2A receptor residues Phe339(6.51) and Phe340(6.52) with superpotent N-benzyl phenethylamine agonists. Molecular Pharmacology 70: 1956–1964.

Caldicott DG, Bright SJ, Barratt MJ (2013). Nbome: A very different kettle of fish. Med J Aust 199: 322–323.

Casale JF, Hays PA (2012). Characterization of Eleven 2,5-Dimethoxy-N-(2-methoxybenzyl)phenethylamine (NBOMe) Derivatives and Differentiation from their 3- and 4-Methoxybenzyl Analogues - Part I. Microgram 9(2): 84-109.

Catlow BJ, Song S, Paredes DA, Kirstein CL, Sanchez-Ramos J (2013). Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning. Exp Brain Res 228: 481–491.

Drug Enforcement Administration (2013). '2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25I-NBOMe; 2C-I-NBOMe; 25I; Cimbi-5), 2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25C-NBOMe; 2CC-NBOMe; 25C; Cimbi-82) and 2-(4-bromo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25B-NBOMe; 2C-B-NBOMe; 25B; Cimbi-36). Background information and evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for temporary scheduling.
http://www.regulations.gov/contentStreamer?objectId=090000648147faf9&disposition=attachment&contentType=pdf

Drugs Forum: http://www.drugs-forum.com/forum/showwiki.php?title=25I-NBOMe

Egan CT, Herrick-Davis K, Miller K, Glennon RA, Teitler M (1998). Agonist activity of LSD and lisuride at cloned 5HT$_{2A}$ and 5HT$_{2C}$ receptors. Psychopharmacology 136: 409–414

Erowid: http://www.erowid.org/chemicals/2ci_nbome

Ettrup A, Hansen M, Santini MA, Paine J, Gillings N, Palner M, Lehel S, Herth MM, Madsen J, Kristensen J, Begtrup M, Knudsen GM (2011). Radiosynthesis and in vivo evaluation of a series of substituted ^{11}C phenethylamines as 5-HT$_{2A}$ agonist PET tracers. European Journal of Nuclear Medicine and Molecular Imaging 38: 681–693.

Ettrup A, Palner M, Gillings N, Santini MA, Hansen M, Kornum BR, Rasmussen LK, Någren K, Madsen J, Begtrup M, Knudsen GM (2010). Radiosynthesis and evaluation of ^{11}C-CIMBI-5 as a 5-HT$_{2A}$ receptor agonist radioligand for PET. Journal of Nuclear Medicine 51: 1763–1770.

Gillings N (2009). A restricted access material for rapid analysis of [^{11}C]-labeled radiopharmaceuticals and their metabolites in plasma. Nuclear Medicine and Biology 36: 961–965

González-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, Lira A, Bradley-Moore M, Ge Y, Zhou Q, Sealfon SC, Gingrich JA (2007). Hallucinogens recruit specific cortical 5-HT$_{2A}$ receptor-mediated signalling pathways to affect behaviour. Neuron 53: 439–452.

Halberstadt AL, Geyer MA (2013). Effects of the hallucinogen 2,5-dimethoxy-4-iodophenethylamine (2C-I) and superpotent N-benzyl derivatives on the head twitch response. Neuropharmacology 77C: 200–207.

Hanks JB, González-Maeso J (2013). Animal models of serotonergic psychedelics. American Chemical Society Chemical Neuroscience 16: 33-42.

Hansen M, Phonekeo K, Paine JS, Leth-Petersen S, Begtrup M, Bräuner-Osborne H, Kristensen JL (2014). Synthesis and structure-activity relationships of N-benzyl phenethylamines as 5-HT$_{2A/2C}$ agonists. ACS Chem. Neurosci. dx.doi.org/10.1021/cn400216u [Epub ahead of print].

Heim R (2003). Synthese und Pharmakologie potenter 5-HT$_{2A}$-Rezeptoragonisten mit N-2-Methoxybenzyl-Partialstruktur. Free Universität Berlin. [Thesis].

Hill SL, Doris T, Gurung S, Katebe S, Lomas A, Dunn M, Blain P, Thomas SH (2013). Severe clinical toxicity associated with analytically confirmed recreational use of 25I-NBOMe: case series. Clinical Toxicology 51: 487–92.

Kelly A, Eisenga B, Riley B, Judge B (2012). Case series of 25I-NBOMe exposures with laboratory confirmation. Clinical Toxicology 50: 702.

Lawn W, Barratt M, Williams M, Horne A, Winstock A (2014). The NBOMe hallucinogenic drug series: Patterns of use, characteristics of users and self-reported effects in a large international sample. J Psychopharmacol 1-9 doi: 10.1177/0269881114523866 [Epub ahead of print].

Marek GJ, Aghajanian GK (1996). LSD and the phenethylamine hallucinogen DOI are potent partial agonists at 5-HT_{2A} receptors on interneurons in rat piriform cortex. Journal of Pharmacology and Experimental Therapeutics 278: 1373–1382.

Nichols DE, Frescas SP, Chemel BR, Rehder KS, Zhong D, Lewin AH (2008). High specific activity tritium-labeled N-(2- methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine (INBMeO): A high-affinity 5- HT_{2A} receptor-selective agonist radioligand. Bioorganic & Medicinal Chemistry 16: 6116–6123.

Poklis JL, Devers KG, Arbefeville EF, Pearson JM, Houston E, Poklis A (2013). Postmortem detection of 25I-NBOMe [2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine] in fluids and tissues determined by high performance liquid chromatography with tandem mass spectrometry from a traumatic death. Forensic Science International. doi:10.1016/j.forsciint.2013.10.015. [Epub ahead of print].

Poklis JL, Clay DJ, Poklis A (2014). High-Performance Liquid Chromatography with Tandem Mass Spectrometry for the Determination of Nine Hallucinogenic 25-NBOMe Designer Drugs in Urine Specimens. J Anal Toxicol Feb 16. [Epub ahead of print].

Poklis JL, Charles J, Wolf CE, Poklis A (2013). High-performance liquid chromatography tandem mass spectrometry method for the determination of 2CC-NBOMe and 25I-NBOMe in human serum. Biomed Chromatogr Jul 25. doi: 10.1002/bmc.2999. [Epub ahead of print].

Rose RS, Cumpston KL, Stromberg PE, Wills BK (2012). Severe poisoning following self-reported use of 25-I, a novel substituted amphetamine. Clinical Toxicology 50: 707.

Rose SR, Poklis JL, Poklis A (2013). A case of 25I-NBOMe (25-I) intoxication: a new potent 5-HT2A agonist designer drug. Clinical Toxicology 51: 174–177.

Soh YNA, Elliott S (2014). An investigation of the stability of emerging new psychoactive substances. Drug Testing Analysis. doi: 10.1002/dta.1576 [Epub ahead of print].

Stellpflug SJ, Kealey SE, Hegarty CB, Janis GC (2013). 2-(4-Iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe): Clinical case with unique confirmatory testing. Journal of Medical Toxicology. doi:10.1007/s13181-013-0314-y [Epub ahead of print].

Telegraph Australia 2012

http://www.dailytelegraph.com.au/news/national/new-hallucinogenic-drug-25b-nbome-and-25i-nbome-led-to-south-australian-mans-bizarre-death/story-fndo2izk-1226472672220.

Telegraph Australia 2013
http://www.dailytelegraph.com.au/newslocal/northern-beaches/police-warning-on-drug-that-killed-a-teenager-in-june/story-fngr8hax-1226765910968

The Australian 2013
http://www.theaustralian.com.au/news/nation/drug-link-to-sydney-teenagers-death-fall/story-e6frg6nf-1226658496485

Walterscheid JP, Phillips GT, Lopez AE, Gonsoulin ML, Chen HH, Sanchez LA (2014). Pathological Findings in 2 Cases of Fatal 25I-NBOMe Toxicity. Am J Forensic Med Pathol 35(1): 20-25.

Annex 1
Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of 25I-NBOMe

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

A total of 62 Member States answered the questionnaire for **25I NBOMe**. Of these only 22 respondents (AMR 4, EUR 15, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that 25I 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 research and as analytical standards. There was no use stated in animal/veterinary care

HARMFUL USE

Eighteen respondents stated that there was recreational/harmful use of 25I NBOMe**.** Common route of administration was oral in 11 responses and oral, inhaling/sniffing in three. Twelve respondents stated the substance was obtained only via trafficking, 1 via diversion and trafficking and in 1 through clandestine manufacturing. Ten respondents reported on the common formulations available with 5 reporting powder, 3 powder and liquid, 1 powder and tablet and 1 tablet forms. Nine respondents also described use on blotter paper. The use is by the general population and in clubs in 2 responses, 4 only in clubs and 3 only in the 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 25I NBOMe. One respondent reported 1 death in 2012 due to 25I NBOMe and both 25 I and 25 C in one death in 2013. Four emergency room visits in 2012 and 13 in 2013 were reported. Other suspected, but not proven, deaths and emergency admissions are also reported. (See also information provided for 25 B and C NBOME, these may have similar effects)

Additional information provided ‘a variety of 2-methoxybenzyl analogues of 2C compounds have been available over the Internet since 2010 (Zuba & Sekula, 2012; Zuba et al., 2013), and the first identified domestic law enforcement encounter with 25I-NBOMe occurred in June of 2011 in Milwaukee, Wisconsin. Since that time, the number of encounters involving 25I-NBOMe, 25C-NBOMe and 25B-NBOMe has steadily increased, reflecting the increased abuse of these substances. Throughout 2012 and 2013, in the United States, there has been a significant increase in availability, trafficking and abuse of 25I-NBOMe, 25C-NBOMe and 25B-NBOMe, evident from the increasing number of encounters reported by forensic laboratories and continued reports toxicity and death reported by emergency departments and medical examiners. Evidence of abuse of 25I-NBOMe initially appeared in 2011, and evidence of abuse of 25C-NBOMe and 25B-NBOMe appeared in 2012.These substances began showing up in forensic laboratory reports on drug seizures 2011. From November 2011 through March 2013 according to the DEA’s System to Retrieve Information on Drug Evidence (STRIDE) data, there are 54 exhibits involving 27 cases for 25I-NBOMe, 27 exhibits involving 12 cases for 25C-NBOMe and 3 exhibits involving 3 cases for 25B-NBOMe. From June 2011 through March 2013, the National Forensic Laboratory Information

System (NFLIS) registered hundreds of reports containing these synthetic substances (25I-NBOMe – 582 reports; 25C-NBOMe – 94 reports; 25B-NBOMe – 13 reports) from all reporting local, state and other federal forensic laboratories in the U.S. 25I-NBOMe, 25C-NBOMe, and 25B-NBOMe were not reported to NFLIS prior to June of 2011, and the number of reports for these substances increased in every quarter of 2012, and in the first quarter of 2013.Law enforcement reports, discussions on Internet forum websites, and personal communications confirm that these substances are commonly purported to be other Schedule I hallucinogens like LSD, psilocin, and 2C-B. Users and sellers have reported they believed they were abusing and trafficking LSD, although subsequent laboratory analysis revealed the blotter papers, liquids, or powders contain some combination of 25I-NBOMe, 25C-NBOMe and 25B-NBOMe instead. Bulk quantities of powdered 25I-NBOMe, 25C-NBOMe and 25B-NBOMe have been seized from shipments originating overseas, particularly from Asia (Customs and Border Protection Data).Thirteen deaths in the U.S. have been associated with 25I-NBOMe through official toxicology reports. Drug induced toxicity and violent, erratic behavior due to the abuse of 25I-NBOMe, 25C-NBOMe and 25B-NBOMe synthetic substances has led to numerous reports of emergency department admissions and deaths (Kelly et al., 2012; Rose et al., 2012; Rose et al., 2013; Hill et al., 2013; Stellpflug et al., 2013).Deaths have been reported for most routes of administration, including nasal insufflation, liquid solutions applied to nasal membrane, sublingual or buccal administration of blotter paper, and consumption of adulterated food items. Youth appear to be the primary abusers of these synthetic substances, as supported by the available emergency department reports and reports of death. The average age of decedents where 25I-NBOMe, 25C-NBOMe or 25B-NBOMe was confirmed to be a contributing factor in the death is 20 years (n=14).'

CONTROL

A total of 17 respondents reported that 25I NBOMe was controlled under legislation that was intended to regulate its availability - nine under "controlled substance act", three under "medicines law", three "temporary ban", one "analogue legislation" and one under "other" legislation. Five countries stated that there were problems with the implementation of this legislation. On illicit activities involving 25I NBOMe, three respondents reported processing into the consumer product, 12 reported trafficking, two diversion and 12 an internet market. Details on seizures are presented below.

	2011 (number of respondents)	**2012 (number of respondents)**
Total number of seizures	10 (1)	466 (10)
Total quantity seized (kg)	No data	0.015(2) (42.4 g in 2013)
Total quantity seized (other)	No data	1,333 blotters (5) 23 g stamp (1)

IMPACT OF SCHEDULING

Twenty out of 22 respondents reported that if 25I NBOMe was placed under international control, they would have the laboratory capacity to identify the substance. There is no reported medical use