



European Monitoring Centre
for Drugs and Drug Addiction

Annex 2. Technical Report on 2-(4-iodo-2,5-dimethoxyphenyl)- N-(2-methoxybenzyl)ethanamine (25I-NBOMe)

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This Technical Report was prepared under EMCDDA contract. Given the time frame stipulated in the Council Decision, it has not been formally edited by the EMCDDA. As a result, while the scientific data presented has been verified to the extent possible, minor changes may be introduced at a later date when the report is officially published. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The Risk Assessment Report on 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25I-NBOMe), to which this report is annexed was produced by the by the Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

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Summary

25I-NBOMe is a substituted phenethylamine, a synthetic derivative of the classical hallucinogen 2C-I which was subject to a risk assessment at European level in 2003. Apart from its use as an analytical reference standard and its use in scientific research, radiolabelled 25I-NBOMe has been used to study the serotonergic system in the brain. 25I-NBOMe has no known legitimate uses as an industrial, cosmetic or medicinal compound.

There has been evidence of the availability of 25I-NBOMe in Europe since 2012, with detections ⁽¹⁾ reported in 23 Member States and Norway. 25I-NBOMe was first detected within the European Union in 2012 with formal notification to the European Union Early Warning System (hereafter 'Early Warning System') in May 2012 by the Swedish National Focal Point.

The "25I" component within 25I-NBOMe refers to the location of the iodine atom on the phenethylamine nucleus. The "NBOMe" component refers to the *N*-(2-methoxybenzyl) part of the molecule. There are a number of other "NBOMe" derivatives that have been notified to the Early Warning System. These include: 25B-NBOMe, 25C-NBOMe, 25H-NBOMe, 25E-NBOMe, 25N-NBOMe, 25D-NBOMe, 25iP-NBOMe, 25G-NBOMe, 25B-N(BOMe)₂, 25I-NBMD, C30-NBOMe, and RH-34.

There appear to be no co-ordinated national or European population surveys on the prevalence of 25I-NBOMe use. There are reports from targeted surveys describing the characteristics of users mostly from the United Kingdom, Australia and the United States. The most common source for the drug was a website.

25I-NBOMe has typically been encountered in the form of 'blotters' or paper 'trips', which are often printed with distinctive designs and perforated so they can be torn into small, single-dose units. There are also reports of seizures in powder, including capsules containing powder, and in liquid form. It is used predominantly by sublingual and buccal administration (blotters), there are also reports of nasal (insufflation and absorption of liquid solutions), oral, injection (intravenous and intramuscular), rectal and smoking. Single use doses for sublingual administration of 25I-NBOMe reported by users are typically in the μg range and may vary from 750 μg to 3750 μg .

Although increasing knowledge is emerging about the *in vitro* and *in vivo* properties of 25I-NBOMe, it is difficult to predict with accuracy any particular potential drug interactions or contraindications. However, its high potency to activate 5-HT_{2A} receptors may be relevant when considering potential interactions with other serotonergic drugs. The concomitant use of medicinal and/or recreational substances known to increase 5-HT-release may increase the risk of developing serotonergic toxicity, the symptoms of which can include tachycardia, hypertension, hyperthermia, muscle rigidity and convulsions. The high potency of 25I-NBOMe and the fact that it is therefore used in μg doses may increase the risk that users are exposed to excessive doses.

(1) 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).

There have been 32 non-fatal intoxications reported by the Member States to the Early Warning System: Belgium (3 cases), Poland (4), Sweden (18), and the United Kingdom (7); analytical confirmation of 25I-NBOMe from biological samples has been reported in 15 of these cases: Belgium 3, Sweden 5, and United Kingdom 7. Data from these cases, along with information from case reports in the scientific and medical literature from Europe and the United States and Australia, indicate that sympathomimetic features including tachycardia, agitation, hallucinations, hypertension and seizures were commonly encountered.

There are no data from animal or human studies on the dependence liability of 25I-NBOMe. There have been 2 deaths reported by the Member States to the Early Warning System where 25I-NBOMe has been detected in post mortem toxicological screening: Belgium (1 death) and the United Kingdom (1). It should be noted that in one of the cases other controlled and non-controlled drugs were also detected and therefore may have contributed to and/or been responsible for death.

There have been no reports of anti-social behaviour related to the use of 25I-NBOMe. There have been three cases of detection of 25I-NBOMe in cases of other types of crimes.

25I-NBOMe has been sold to users 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 and consequently, populations using LSD may also be at risk of exposure to 25I-NBOMe.

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25I-NBOMe) is a synthetic derivative of the classical hallucinogen 2-(4-iodo-2,5-dimethoxyphenyl)ethanamine, also known as 4-iodo-2,5-dimethoxyphenethylamine or 2C-I which was subject to a risk assessment at European level in 2003 (EMCDDA, 2004). The "I" in 2C-I and 25I-NBOMe denotes the presence of an iodine atom in the 4-position of the phenyl ring (Figure 1). The systematic (International Union of Pure and Applied Chemistry, IUPAC) name is 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine. Other names that may be encountered and Chemical Abstract Service (CAS) registry numbers are given in Tables 1 and 2, respectively.

Table 1. Frequently encountered names for 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine.

Alternative chemical names

4-Iodo-2,5-dimethoxy-*N*-(2-methoxybenzyl)phenethylamine
4-Iodo-2,5-dimethoxy-*N*-[(2-methoxyphenyl)methyl]-benzeneethanamine
N-(2-Methoxybenzyl)-4-iodo-2,5-dimethoxyphenethylamine
2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethan-1-amine
N-(2-Methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine
4-Iodo-2,5-dimethoxy-*N*-(*o*-methoxybenzyl)phenethylamine

Abbreviations that may be encountered

25I-NBOMe; NBOMe-2C-I; 2CINBOMe; 25I; NBOMe-2CI; 2C-I-NBOMe; 2C-I-NBOMe; Cimbi-5⁽²⁾, Cimbi-5-2⁽³⁾, INBMeO⁽⁴⁾

The "25I" component within 25I-NBOMe refers to the location of substituents on the phenethylamine nucleus and points towards the 2,5-dimethoxy pattern. The location of the iodine atom is normally associated with the 4-position (Figure 1) which reflects historical developments explored by Shulgin and colleagues since the 1960s (Brandt, 2014). The "NBOMe" component refers to the *N*-(2-methoxybenzyl) part of the molecule (Figure 1). Two more isomers are possible that carry the methoxyl group on positions 3- or 4- of the benzyl ring which means that the "NBOMe" abbreviation could be ambiguous with regards to their position. Positional isomers may include those with modified positions on the phenyl ring (for example, found in the "ψ"-analogue 26I-NBOMe). It is currently not known, however, whether these two isomers have also been encountered as recreationally used substances.

⁽²⁾ [¹¹C]CIMBI-5. Radiolabelled version (¹¹C on *N*-(2-OCH₃)benzyl) used for PET scanning - Center for Integrated Molecular Brain Imaging (CIMBI).

⁽³⁾ [¹¹C]CIMBI-5-2. Radiolabelled version with (2-O¹¹CH₃) group on phenyl ring also evaluated for PET scanning.

⁽⁴⁾ Radiolabelled *N*-(2-[³H-OCH₃]benzyl)-2-[³H-OCH₃] version of 25I-NBOMe ([³H]INBMeO) used as radioligand for binding studies.

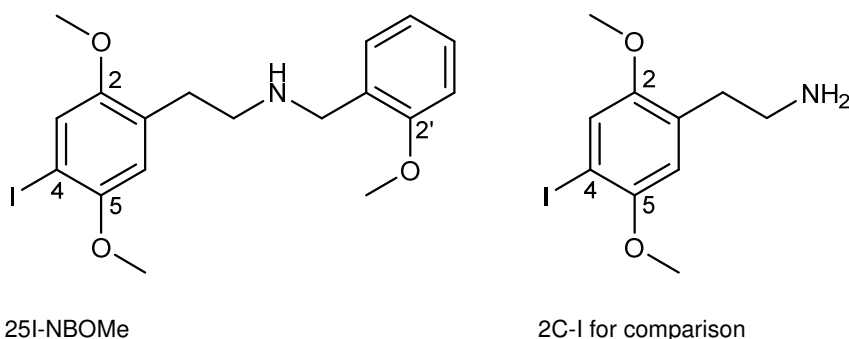
One suggestion for differentiation between these particular isomers was provided recently where the position of the substituent would be explicitly indicated in the abbreviated name which gave, for example, 25I-NB2OMe rather than 25I-NBOMe when referring to *N*-(2-methoxybenzyl) (Casale and Hays, 2012).

Reported street names include: '25I', 'dots', 'legal acid', 'solaris', 'cimbi-5', 'NBomb', 'NE-BOME', 'smiles', 'INBMeO', 'BOM-Cl', 'Hoffman' and 'N-boom'.

Table 2. Chemical Abstract Service (CAS) Registry Numbers for 25I-NBOMe

CAS Registry Numbers	Variant
919797-19-6	Free base
1043868-97-8	Hydrochloride salt
1248338-50-2	<i>N</i> -(2- ¹¹ CH ₃ O)benzyl free base
1043869-41-5	<i>N</i> -(2-C ³ H ₃ O)benzyl free base
1404305-56-1	(2- ¹¹ CH ₃ O) free base

Figure 1. The numbered molecular structure, formula, relative molecular weight and monoisotopic mass of 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25I-NBOMe).



Molecular formula: C₁₈H₂₂I NO₃

Molecular weight: 427.28 g/mol (base)

Monoisotopic mass: 427.0644 Da

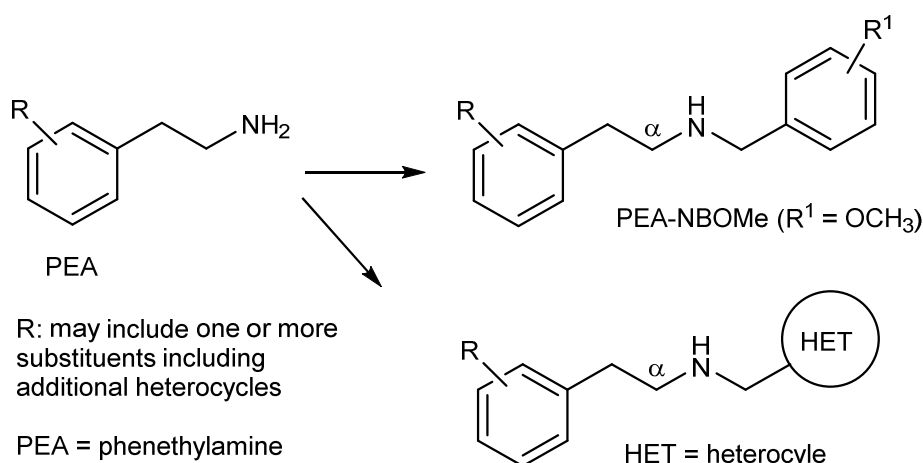
As of 7 March 2014, twelve "NBOMe"-type compounds have been notified to the EU Early Warning System. Nine of them are "NBOMe" analogues in the traditional sense where the amine side chain is connected to the *N*-(2-methoxybenzyl) moiety. One was represented by the dialkylation product (*N*-(2-methoxybenzyl)₂) leading to 25B-N(BOMe)₂. Two notified analogues were reported to carry another substituent on the amine side chain, i.e. *N*-(3,4,5-trimethoxybenzyl) and *N*-(2,3-methylenedioxyphenyl), although the exact position of the latter methylenedioxy substituent was not verified by nuclear magnetic resonance spectroscopy (NMR) analysis and could be a 3,4-methylenedioxy isomer. The structural diversity of NBOMe compounds may arise from the potential to modify the structural backbone at various locations. Obvious examples may include (Figure 2):

a) the phenyl ring of the phenethylamine (PEA). Notifications to the EU Early Warning System are currently limited to analogues with a modified substituent present at the 4-position. Seven of eight additional analogues (25I-NBOMe excluded) mentioned above carry an alternative substituent, i.e. bromine (25B-NBOMe), chlorine (25C-NBOMe), hydrogen (25H-NBOMe), ethyl (25E-NBOMe), nitro (25N-NBOMe), methyl (25D-NBOMe) or isopropyl (25iP-NBOMe), respectively, whereas the 2,5-dimethoxy-3,4-dimethylphenyl analogue was represented as 25G-NBOMe. The phenethylamine nucleus may also be replaced by their corresponding amphetamine (methyl group present at the α -carbon), tryptamine, benzofuran (saturated or unsaturated), benzodifurans, or cathinone counterparts but these possibilities have not yet been encountered in the context of the EU Early Warning System. Recently, RH-34 (3-[2-(2-methoxybenzylamino)ethyl]-1H-quinazoline-2,4-dione) containing a quinazolidinedione moiety was reported by two Member States.

b) the *N*-benzyl group. Examples already reported to the EU Early Warning System, mentioned above, are *N*-(2,3-methylenedioxyphenyl) (25I-NBMD) or an 3,4-methylenedioxyphenyl analogue and *N*-(3,4,5-trimethoxybenzyl) (C30-NBOMe). It is worth noting that both structural elements, i.e. the PEA and the *N*-benzyl components, may be modified at the same time as well. For example, 25I-NBMD maintained the "25I" pattern while showing a modified "NBOMe", whereas C30-NBOMe revealed the presence of "25C" and a modified "NBOMe".

c) replacement of the *N*-benzyl ring with a range of other heterocycles. While many examples exist in the scientific literature, e.g. (Braden, 2007, Hansen, 2010, Nichols, 2012), notifications to the EU Early Warning System have not yet been received.

Figure 2. Structural flexibility for "NBOMe"-type substances. Further modifications may also include substitutions at the α -carbon of the ethylamine side chain.



Identification and analytical profile

The first ^1H and ^{13}C nuclear magnetic resonance spectroscopy data (NMR) and electron ionisation (EI) mass spectrum (fragments included M^{*+} at m/z 427, base peak at m/z 121, m/z 150 (61%) and m/z 91 (42%)) were published in 2003 (Heim, 2003). A Fourier transform infrared (FTIR) spectrum was reported in 2012 (Casale and Hays, 2012).

Extraction and direct analysis of 25I-NBOMe (e.g. as a powder or in liquid form) can be carried out in a straightforward manner using standard techniques. Detection in biological fluids, however, may require the implementation of very sensitive techniques, such as tandem mass-spectrometry, due to low concentrations commonly encountered in the sample matrices. 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 several case studies (e.g. Casale and Hays, 2012, Gillings, 2009, Hill et al., 2013, Poklis et al., 2013, Poklis et al., 2014b, Rose et al., 2013, Soh and Elliott, 2013, Stellpflug et al., 2013, Walterscheid et al., 2014).

The detection output depends on the technique used but for 25I-NBOMe with positive mode LC-MS, the protonated molecule $[\text{M}+\text{H}]^+$ is observed at m/z 428 with commonly observed product ions at m/z 121 m/z ion (*N*-(2-methoxy)benzyl fragment) as well as m/z 91 which represents the tropylium species (Hill, et al., 2013, Poklis, et al., 2013, Poklis, et al., 2014b, Rose, et al., 2013, Soh and Elliott, 2013, Stellpflug, et al., 2013, Walterscheid, et al., 2014). Presumptive test data (including Marquis field tests) have not been published and data on cross-reactivity with commercially available urine immunoassay tests used for standard drugs of abuse are currently unavailable.

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS Registry Numbers listed above and no information was found.

Physical description

The free base is a colourless oil (Heim, 2003) whereas the hydrochloride salt is a white, water soluble powder with reported melting points of 166 °C ($\text{Et}_2\text{O}/i\text{PrOH}\cdot\text{HCl}$) (Heim, 2003) and 162-166 °C ($\text{Et}_2\text{O}/\text{EtOH}\cdot\text{HCl}$) (Hansen, 2010, Hansen et al., 2014), respectively.

It has been reported that some Internet retailers ⁽⁵⁾ have advertised 25I-NBOMe as the free base and also as a hydroxypropyl- β -cyclodextrin (HPBCD) complex. In both cases, no reports have been received by the EMCDDA that have analytically confirmed the base/salt form or the presence of 25I-NBOMe in complex with HPBCD, although it is uncertain whether this would necessarily be detected with routine analytical techniques. Information provided from seizures and collected samples have noted the presence of 25I-NBOMe in blotters (small paper doses for sublingual/buccal administration), powders, powder-filled capsules and liquids (EMCDDA–Europol, 2014). Analytical reference standards are

⁽⁵⁾ The term 'Internet retailers' is used in this report to describe Internet shops that offer new psychoactive substances for sale often advertised as 'legal highs' and 'research chemicals'.

commercially available ⁽⁶⁾. See section A1.2 for a description of the physical forms reported.

Methods and chemical precursors used for the manufacture of 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine

There is currently no information regarding manufacturing sites, the chemical precursors or the synthetic routes used for the 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine that has been detected on the drug market.

The synthesis of 25I-NBOMe was first published in 2003 and was based on a classical reductive alkylation procedure (Abdel-Magid et al., 1996) where the primary amine starting material, i.e. 2C-I in this particular case, was reacted with 2-methoxybenzaldehyde to give an imine intermediate. Once this was formed, a reducing agent (in this case NaBH₄) was employed to yield 25I-NBOMe (Heim, 2003). Several researchers have used the same process to prepare a variety of NBOMe analogues (Casale and Hays, 2012, Hansen, et al., 2014, Heim, 2003). Several variations have been published in 1994 for the preparation of 2-(4-bromo-2,5-dimethoxyphenyl)ethanamine (2C-B) and 5-methoxytryptamine-based NBOMe analogues. The primary amine also served as the starting material and side chain modifications included the reaction with a corresponding benzoyl halide or benzoic acid. The reduction was carried out using several different reducing agents (Glennon et al., 1994).

Typical impurities encountered in seized and collected samples

Detailed information with regards to route-specific by-products produced during the synthesis of 25I-NBOMe is currently not available. In addition there is no data currently available on the impurities detected in seized and collected samples. However, reductive alkylation reductions can suffer from a range of side reactions and one mechanism may be typically observed is the formation of dialkylated by-products (Baxter and Reitz, 2002). Indeed, one European country (Hungary) reported the seizure of 142 blotters in October 2013. Analysis revealed the presence of 25B-NBOMe traces only, which would have been the expected substance. However, the main product found was the *N,N*-dibenzylated product, i.e. 25B-N(BOMe)₂, which pointed towards the fact that the synthesis (presumably attempting the *N*-monobenylation of the amino group of 2C-B) did not proceed as planned (EMCDDA, 2013). Whether the dialkylated product was used with or without the knowledge of the manufacturers is not known. Another likely by-product that may be expected is the imine intermediate which is formed in the first instance when the primary amine starting material undergoes condensation following reaction with the corresponding benzaldehyde reagent. The presence of the imine, either as a trace or the main component, would then point towards an incomplete reduction. So far, data about the presence of imine traces in seized material are not available.

Twenty-three Member States (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland,

⁽⁶⁾ For example <https://www.caymanchem.com/app/template/Product.vm/catalog/9001128/promo/emolecules>; and, http://www.lgcstandards.com/epages/LGC.sf/en_GB/?ObjectPath=/Shops/LGC/Products/CAY-9001128-10MG

Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom) and Norway reported detections of 25I-NBOMe ⁽⁷⁾. In most cases, 25I-NBOMe was reported as the only active substance. However, in about 10% of detections it was found in combination with other substances, including other "NBOMe" compounds (25B-NBOMe, 25C-NBOMe, 25H-NBOMe, 25N-NBOMe, 25C-NBOMe), 2C-B, 2C-C, 2C-I, 2C-T-4, mescaline, LSD (lysergic acid diethylamide), MDPBP (a synthetic cathinone), JWH-122 *N*-(4-pentenyl) analogue and an unknown substance. No quantitative analyses were available (EMCDDA–Europol, 2014).

A1.2. Physical/pharmaceutical form

Reports of seizures and collected samples have noted that 25I-NBOMe has typically been in the form of 'blotters' or paper 'trips'. These are sheets of absorbent paper designed for sublingual or buccal administration. They are often printed with distinctive designs and perforated so they can be torn into small, single-dose units (typically approximately 7 mm x 7 mm square). There are also reports of seizures in powder (including two seizures of capsules containing powder) and in liquid form (5% of cases). The blotter formulation has traditionally been reserved for substances that show high potency *in vivo* with the internationally controlled hallucinogenic substance LSD being encountered most frequently in that form. There is some suggestion that 25I-NBOMe has been sold as a replacement for LSD. Seized 25I-NBOMe blotters varied in size (from 5 to 10 mm square), colour, and design (e.g. smiley, Felix the cat, Mickey Mouse, Rolling Stones tongue logo, Hoffman bicycle, etc.) (EMCDDA–Europol, 2014). See section C and Appendix 1 for further details of the seized and collected samples of 25I-NBOMe.

A1.3. Route 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 Erowid include: '750 µg, sublingual'; '3750 µg, sublingual'; '1000 µg, sublingual'; '1 mg, buccal'; '1 blotter hit, sublingual/buccal'; '1000 µg, insufflated'; '500-1000 µg, smoked' (Erowid, 2014a). 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 substances (Bluelight Forum, 2014, Drugs-Forum, 2014, Erowid, 2014a).

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacodynamics

⁽⁷⁾ 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

The ability of 25I-NBOMe to affect the 5-HT_{2A} receptor originally derived from vascular preparations used to determine 5-HT_{2A} mediated contractile effects in the rat tail artery. 25I-NBOMe was found to act as a partial agonist ($E_{max} = 30\%$ relative to 5-HT) but appeared to be about 1240 times more potent than 5-HT in eliciting vasoconstriction. The 5-HT_{2A} receptor antagonist ketanserin antagonised the effects of 25I-NBOMe (Heim and Elz, 2000). Further studies and comparison with a range of other "NBOMe" analogues confirmed that 25I-NBOMe was the most potent ($EC_{50} = 81 \text{ pM}$) 5-HT_{2A} receptor agonist under the *in-vitro* conditions tested (Heim, 2003).

Data from a number of additional cell-based *in-vitro* studies have shown that 25I-NBOMe binds with nanomolar affinity to the 5-HT_{2A} receptor (Table 3) and that it is a full agonist with less pronounced subtype selectivity over 5-HT_{2C} (Braden et al., 2006, Ettrup et al., 2011, Ettrup et al., 2010, Hansen, 2010, Hansen, et al., 2014, Nichols, 2012, Nichols et al., 2008). Braden et al. have shown that the addition of the N-(2-methoxybenzyl) group led to a 17-fold increase in binding affinity at the human 5-HT_{2A} receptor when compared to the 2C-I counterpart, whereas potency in functional activity (phosphatidylinositide turnover) increased about 5.7-fold (Braden, et al., 2006). It has been established using other drugs such as mescaline, 2,5-dimethoxy-4-methylamphetamine (DOM), LSD and psilocybin that high affinity binding and activation of the 5-HT_{2A} receptor subtype plays an important role in mediating a variety of effects *in-vitro* and *in-vivo* that have been correlated with psychoactive/hallucinogenic effects in humans such as changes in perception, mood and cognition (Geyer and Vollenweider, 2008, González-Maeso and Sealfon, 2009, Halberstadt and Geyer, 2013, Halberstadt and Nichols, 2010, Hanks and González-Maeso, 2013, Nichols, 2004).

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 (2014) studied the effect of 25I-NBOMe on the head twitch behavioural response (HTR) in mice which is used to indicate the involvement of 5-HT_{2A}-mediated mechanisms (Canal and Morgan, 2012, Hanks and González-Maeso, 2013). Consistent with observations made with other serotonergic hallucinogens, it was found that 25I-NBOMe produced a robust and potent HTR in mice which was antagonised by the potent 5-HT_{2A} receptor antagonist MDL100,907 (volinanserin). Interestingly, 25I-NBOMe ($ED_{50} = 78 \text{ }\mu\text{g/kg}$, i.e. $0.17 \text{ }\mu\text{mol/kg}$) was only slightly less potent than LSD ($ED_{50} = 52.9 \text{ }\mu\text{g/kg}$, i.e. $0.13 \text{ }\mu\text{mol/kg}$).

In comparison, 2C-I ($ED_{50} = 830 \text{ }\mu\text{g/kg}$, i.e. $2.42 \text{ }\mu\text{mol/kg}$) was observed to be ten-fold less potent than 25I-NBOMe to induce the HTR in male C57BL/6J mice (Halberstadt and Geyer, 2014). Separately, 25I-NBOMe was used in a psilocybin experiment in mice to study neurogenesis and the extinction of trace fear conditioning. While low-dose (0.1 and 0.5 mg/kg) psilocybin (intraperitoneal injection) led to the extinction of a classically conditioned fear response and a trend towards increased hippocampal neurogenesis (not statistically significant), administration of high-dose (1.0 mg/kg) psilocybin, ketanserin (both showed no impact on extinction) or 25I-NBOMe was observed to decrease formation of new neurons based on immunofluorescence studies of cell proliferation (Catlow et al., 2013). How this relates to humans, however, remains to be investigated in more detail.

Interactions with other drugs or medicines

Although increasing knowledge is emerging about the *in vitro* and *in vivo* properties of 25I-NBOMe, it is difficult to predict with accuracy any particular potential drug interactions or contraindications. However, as stated above, the high potency to activate 5-HT_{2A} receptors may be relevant when considering potential interactions with other serotonergic drugs. The concomitant use of medicinal products (e.g. selective serotonin reuptake inhibitors (SSRIs)) and/or recreational substances known to increase 5-HT-release, may increase the risk of developing serotonergic toxicity (often also referred to as serotonin syndrome), the

symptoms of which can include tachycardia, hypertension, hyperthermia, muscle rigidity and convulsions (Boyer and Shannon, 2005, Isbister et al., 2007, Sternbach, 1991). Since the high potency of 25I-NBOMe and the fact that it is therefore used in μg doses increase the risk that users may be exposed to excessive doses, there is the potential that additional mechanisms may be triggered in addition to those that are directly triggered by 5-HT_{2A} agonism (e.g. Table 3).

Pharmacokinetics

Published pharmacokinetic data for 25I-NBOMe in animals are currently not available and whilst there do not appear to be any published pharmacokinetic data for 25I-NBOMe in humans either, 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 (2013) reported the presumed detection of a desmethyl- metabolite of 25C-NBOMe. While the *N*-(2-hydroxybenzyl) analogue has been recently shown to be potent 5-HT receptor ligands (Hansen et al., 2014), further research is required to confirm the extent to which these may form during metabolism. Both studies revealed the presence of 25H-NBOMe, i.e. the de-iodinated analogue, although further studies are needed to clarify whether it was formed during metabolism or whether it was present as a contaminant in the consumed product. A recently published *in vitro* study provided insights into the behaviour of a range of "NBOMe" analogues and their primary amine (2C-X) counterparts ⁽⁸⁾ in human microsomal stability assays. The principle behind this study was the determination of intrinsic

⁽⁸⁾ With X = I, CH₃, SEt, Br, CN, SPr, CF₃, SMe, Cl and H (Leth-Petersen et al. 2014).

Table 3. Binding data 25I-NBOMe (nM affinity)

Receptor	(Braden, 2007, Braden, et al., 2006, Nichols, 2012) (K_i)	(Nichols, et al., 2008) (K_d)	(Ettrup, et al., 2011, Ettrup, et al., 2010, Hansen, 2010) (K_i)	(Hansen, et al., 2014) (p K_i)
5-HT _{1A}	1696 ^a	-	85	-
5-HT _{1B}	-	-	3742	-
5-HT _{1D}	-	-	-	-
5-HT _{1E}	-	-	-	-
	0.087 ^b	0.097 ^g		
	0.044 ^c	0.15 ^h	2.2 ⁱ	
5-HT _{2A}	0.15 ^d		- _j 1.5 ^k 1.49 ^l	8.67 ^m
5-HT _{2B}	-	-	2.3	-
5-HT _{2C}	0.43 ^e 0.13 ^f	-	7.0	8.15 ⁿ
5-HT ₃	-	-	>10000	-
5-HT _{5A}	-	-	2200	-
5-HT ₆	-	-	58.1	-
5-HT ₇	-	-	1670	-
D1	-	-	3718	-
D2	-	-	1600	-
D3	-	-	117	-
D4	-	-	647	-
D5	-	-	7847	-
Beta1	-	-	-	-
Beta2	-	-	-	-
H1	-	-	-	-
H2	-	-	-	-
H3	-	-	-	-
Sigma 1	-	-	-	-
Sigma 2	-	-	-	-
Alpha 1A	-	-	-	-
Alpha 1B	-	-	-	-
Alpha 1D	-	-	-	-
Alpha 2A	-	-	1106	-
Alpha 2B	-	-	-	-
Alpha 2C	-	-	348	-
DAT	-	-	5031	-
SERT	-	-	1009	-
NET	-	-	4574	-
MOR	-	-	-	-
KOR	-	-	-	-
M1	-	-	>10000	-
M2	-	-	>10000	-
M3	-	-	>10000	-
M4	-	-	>10000	-
M5	-	-	1381	-

^a [³H]8-OH-DPAT as radioligand at h5-HT_{1A}

^b (\pm)-[¹²⁵I]DOI as radioligand at r5-HT_{2A}; PI hydrolysis (r5-HT_{2A}): EC₅₀ 2.50 nM (78% intrinsic activity relative to 5-HT)

^c (\pm)-[¹²⁵I]DOI as radioligand at h5-HT_{2A}; PI hydrolysis (h5-HT_{2A}): EC₅₀ 0.44 nM (81% intrinsic activity relative to 5-HT)

^d [³H]Ketanserin as radioligand at h5-HT_{2A}

^e (\pm)-[¹²⁵I]DOI as radioligand at h5-HT_{2C}

^f (\pm)-[¹²⁵I]DOI as radioligand at r5-HT_{2C}

^g K_d values determined in A20 (A549) cells

^h K_d values determined in Hh2A (HEK) cells. Approximately 60% of sites were labelled by [³H]25I-NBOMe that were labelled by [³H]ketanserin

ⁱ [³H]Ketanserin as radioligand at h5-HT_{2A} according to NIMH-PDSP protocols (NIMH-PDSP)

^j [³H]LSD as radioligand at h5-HT_{2A} according to NIMH-PDSP protocols (NIMH-PDSP)

^k [³H]MDL100907 as radioligand at r5-HT_{2A}; PI hydrolysis (r5-HT_{2A}): ED₅₀ 1.02 nM (85% intrinsic activity relative to 5-HT)

^l [³H]MDL100907 as radioligand at r5-HT_{2A}; PI hydrolysis (r5-HT_{2A}): ED₅₀ 1.02 nM (91% intrinsic activity relative to 10 μ M 5-HT)

^m Hansen: [³H]Ketanserin as radioligand at h5-HT_{2A}; PI hydrolysis (h5-HT_{2A}): pEC₅₀ 9.14 nM (90% intrinsic activity relative to 5-HT). Procedures according to NIMH-PDSP protocols (NIMH-PDSP)

ⁿ [³H]Mesulergine as radioligand at r5-HT_{2C}; PI hydrolysis (h5-HT_{2C}): pEC₅₀ 7.74 nM (101% intrinsic activity relative to 5-HT). Procedures according to NIMH-PDSP protocols (NIMH-PDSP).

clearance (CL_{int}), i.e. to measure the volume of blood from which a particular substance might be cleansed. In this particular case, a clearance rate above human liver blood flow, i.e. 1.3 L/kg/h, would be considered to reflect first pass metabolism. For example, while 2C-I showed an intrinsic clearance of 0.20 L/kg/h, its *N*-(2-methoxybenzyl) derivative 25I-NBOMe revealed an intrinsic clearance of 4.1 L/kg/h which provided a potential explanation for the fact that 2C-I is orally active while 25I-NBOMe would be predicted to be orally inactive as a hallucinogen due to extensive first pass metabolism and insufficient bioavailability (Leth-Petersen et al., 2014). Further studies seem warranted to investigate the issue related to oral activity of 25I-NBOMe and its relationship to dosage levels in more detail (Erowid, 2014b, Lawn et al., 2014).

A3. Psychological and behavioural effects

There are no published studies assessing the psychological and/or behavioural effects of 25I-NBOMe. See section D1.2.1. for a discussion of some of the effects that have been self-reported by users on Internet drug discussion forums. However, in summary, users reported positive and negative psychological and behavioural effects, including; euphoria, change in visual perception, mental and physical stimulation, increased awareness, aphrodisiac and empathic effects, paranoia, fear, panic, unwanted and overwhelming feelings.

A4. Legitimate uses of the product

25I-NBOMe is available as an analytical reference standard and is used in scientific research. Specifically, 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). There are currently no other indications that 25I-NBOMe may be used for other legitimate purposes. There are no known uses of 25I-NBOMe as a component in industrial, cosmetic or agricultural products. There is no information that 25I-NBOMe is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a European Union database on the synthetic routes of all medicinal products this information cannot be verified. There is no marketing authorisation (existing, ongoing or suspended) for 25I-NBOMe neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency (EMCDDA–Europol, 2014).

Section B. Dependence and abuse potential

B1. Animal in vivo and in vitro data

There are no published experimental animal studies that have examined the dependence and abuse potential of 25I-NBOMe.

B2. Human data

There are no published cases in the scientific or grey literature nor user reports describing the potential for dependence or abuse potential for 25I-NBOMe. Additionally, there have been no studies investigating the dependence and/or abuse potential of this substance in humans. Information from local, regional or national drug treatment agencies about the dependence and abuse potential is not available.

Section C. Prevalence of use

Information from seizures, collected and biological samples

The first official notification of 25I-NBOMe to the European Union early warning system was 21 June 2012 by the Swedish national focal point. The Reporting form details a seizure of seven green blotters (paper doses) seized by police in Borlänge on 31 May 2012. The identification was based on gas chromatography-mass spectrometry and a comparison of the mass spectrum with a reference spectrum.

Europol received reports from six Member states with regards to level of production, distribution and trafficking (Belgium, Finland, Germany, Hungary, Poland and Slovakia).

Belgium reported two seizures of 25I-NBOMe that were seized while in transit from China to the Netherlands. In the first case the substance was labelled as "ETHYLENE VAE" (107 g) and in the second case as "EGTAZIC ACID" (51 grams).

Czech Republic reported seizures of 25 (1x1 cm), 95 (0.6x0.6 cm) and 5 blotters with 25I-NBOMe determined as the "main ingredient".

Finland reported that 71 seizures of 25I-NBOMe were made in the first half of 2013. In 68 cases, the substance was seized as blotters (10,004 units in total) and in three cases as liquid (20 ml in total).

Germany reported that 11 seizures of 25I-NBOMe were made between November 2012 and August 2013. The substance was seized in powder form in two cases, as a liquid in three cases and as blotters in six cases. In one seizure involving 10.7 grams of 25I-NBOMe powder that was made in April 2013, it was labelled as "1,2-Di(2-aminoethoxy)-ethaneN,N,N,Ntetraacetic acid". All three seizures of 25I-NBOMe in liquid form were made in June 2013 and ranged from 0.61 grams to 41.4 grams. In the majority of cases, the substance was seized in the form of blotters. 25I-NBOMe was also detected in mixtures with other substances, including: 25H-NBOMe, 25C-NBOMe, JWH-122 *N*-(4-pentenyl) analogue, 2C-H-NBOMe and 2C-C-NBOMe.

Hungary reported "a few" seizures of 25I-NBOMe in powder form and blotter form made since 2012.

Poland reported that 25I-NBOMe had been seized on three occasions, with a total of 48 blotters and "one piece of paper laced with substance" seized.

Slovakia reported one seizure of 25I-NBOMe in the form of a colourless liquid (1 ml). No reports were received that indicated licit or illicit production of 25I-NBOMe in any of these countries.

EMCDDA received reports of detections of 25I-NBOMe ⁽⁹⁾ from twenty-three Member States (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom) and Norway.

As noted before, 25I-NBOMe has typically been seized as 'blotters' or paper 'trips'. Quantities of seized blotters ranged from one single unit (Denmark, Germany, Estonia, Finland, Poland, Slovakia and Norway) to 5154 units (Ireland); Finnish customs reported ten single seizures greater than 500 units. In a smaller number of cases, powders (from 0.025

⁽⁹⁾ 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

grams to 107 grams, Belgium), liquids (from 0.2 ml, Slovenia, to 75.2 grams, Poland) and capsules containing powder (10 units in Finland and 48 units in Norway) were seized.

Finland reported more than half of the total number of seizures between June 2012 and October 2013: 107 seizures from Helsinki airport postal customs and 14 seizures from the police. 25I-NBOMe was seized as blotters in most cases (111 seizures); the quantities seized ranged from a single blotter to 1200 units, with a total of 15796 units. Small quantities were seized in other physical forms: powder (five seizures, ranging from 0.1 to 4.5 grams), liquid (four seizures, from 4 to 12 ml) and capsules containing powder (one seizure of 10 capsules).

Denmark reported ten seizures of blotters (up to 263 units, from April to July 2013) and a seizure of powder (1.5 grams, January 2012).

Germany reported ten seizures made in 2013. These included six seizures of blotters, three seizures of liquids (from 0.61 grams to 41.4 grams) and one powder (10.7 grams, labelled as "1,2Di(2-aminoethoxy)-ethaneN,N,N,Ntetraacetic acid").

In Poland, the first seizure of 25I-NBOMe (reported in 2011) was in liquid form; it has been mostly seized as blotters (up to 391 units) but also in powder form on two occasions (0.4 grams and 5.5 grams).

Sweden detected 25I-NBOMe for the first time in May 2012 when 7 green blotters were seized. It reports a similar number of seizures of blotters and powders (5 to 583 units and 1.49 grams to 13.82 grams, respectively).

Norway reported nine seizures of blotters ranging from 1 to 250 units and one seizure of 48 capsules containing powder.

France, Hungary, Italy and the United Kingdom reported more than five seizures. France reported mostly blotters (in some cases, blotters came in a plastic bag labeled '2 extra stamps') but also one liquid and two powders; most of the seizures were made by customs authorities at Roissy airport (Paris). In Hungary, small quantities of blotters (from 2 to 17 units) and powders (10.66 grams and 12.73 grams) were seized by the police. Italy (from 4 to 52 units) and the United Kingdom (from 3 to 2561 units) reported only seizing 25I-NBOMe in the form of blotters.

Belgium, Estonia, Greece, Ireland, Portugal and Spain reported less than five seizures. Belgian police seized ten blotters and customs authorities at Bierset airport (Liège) reported three seizures of powder, two of 75 grams and one of 107 grams which had arrived from China. Two seizures of blotters were reported by Estonia (one and 299 units) and Greece (2 and 103 units). Ireland reported the biggest single seizure of blotters, totalling 5154 units; Portugal reported four seizures of blotters (from 2 to 50 units) from June to September 2013; and Spain reported three detections of powder with no further details provided.

Seven countries reported one seizure of 25I-NBOMe only: blotters in the Czech Republic (120 units), Latvia (124 units) and Romania (3 units); powder in Lithuania (0.025 grams) and the Netherlands (0.5 grams); and liquids in Slovakia (1 ml) and Slovenia (0.2 ml).

Biological samples

Three Member States (Belgium, Sweden and the United Kingdom) reported detections of 25I-NBOMe in biological samples. These included 15 non-fatal intoxications (Belgium, 3 cases; Sweden, 5; and the United Kingdom, 7) and two deaths, one each in Belgium and in the United Kingdom. The United Kingdom also reported the detection of 25I-NBOMe in three further cases: two criminal suspects in a drug-related death and an intoxicated driver. Further details are provided in Table 7 and the Joint Report on 25I-NBOMe (EMCDDA-Europol 2014).

Collected samples

Five Member States (Austria, Belgium, Italy, the Netherlands and Spain) reported the detection of 25I-NBOMe in collected samples.

Austria reported six samples (all blotters), collected and analysed between February and October 2013 as part of the 'pill'-testing project run by 'ChEckiT!'. In five cases, the samples were sold as LSD and in the remaining case the sample was sold as mescaline. An unknown substance was also detected in one of the samples.

Belgium reported a sample of five blotters collected in August 2013 and January 2014 as part of the investigations into one of the three non-fatal intoxications reported below. The blotters were collected from the patient and were found to contain 25I-NBOMe and traces of 25C-NBOMe.

Italy reported a red blotter with a weight of 20 mg with a logo of a yellow/orange 'smile' collected in the Veneto region. No other substances in addition to 25I-NBOMe were detected.

The Netherlands reported 25I-NBOMe in six collected samples. Four cases involved blotters (amounting to a total of 16 blotters) and two involved samples of powder collected in 2012 and 2013. The samples were sold at consumer level either as 25I-NBOMe (3 cases), LSD (2 cases) or 2C-E (1 case).

Spain reported three samples of blotters containing 25I-NBOMe which were collected at different venues in January 2013.

Further details of these collected samples, including information on the product labels are provided in the Joint Report on 25I-NBOMe (EMCDDA-Europol 2014). Further to this information, seven Member States reported additional 25I-NBOMe detections in the updated Joint Report Questionnaire – Austria (an additional collected sample), Czech Republic (an

additional seizure), Ireland (an additional seizure), Italy (two seizures), Lithuania (additional details on the seizure), Poland (four seizures) and Sweden (12 seizures).

Availability from Internet retailers

This information is currently being collated by the EMCDDA.

Prevalence of use

There are currently no co-ordinated national or European population surveys on the prevalence of 25I-NBOMe (or 25I-NBOMe derivatives) use.

A recently published report described the characteristics of users of 25B-NBOMe, 25C-NBOMe and 25I-NBOMe through the Global Drugs Survey (Lawn, et al., 2014). A total of 22289 responses were collected in late 2012. One-third (n = 7360; 33.9%) of respondents were from the UK, 7784 (35.9%) were from Australia, 3756 (17.3%) were from the USA, 2164 (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 tried it in 2012 and 81.2% of this group administered the drug orally or sublingually/buccally. The majority (n = 296; 56.7%) of NBOMe users in the preceding 12 months were from the USA, 21.3% (n = 111) were from the UK, 10.2% (n = 53) were from the Euro-Zone, 9.8% (n = 51) were from Australia and 2.1% (n = 11) were from Canada. Subjective effects were similar to comparable serotonergic hallucinogens, though greater "negative effects while high" and greater "value for money" were reported. The most common (41.7%) drug source was a website.

The recent report on the "NBOMe" compounds by the Advisory Council on the Misuse of Drugs in the United Kingdom noted that "there was no evidence of significant use in recent self-report user surveys [it is unclear in the report if it refers to 25I-NBOMe or NBOMe compounds in general] (Global Drug Survey, 2013 ⁽¹⁰⁾), although there is 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 (ACMD), 2013). In addition, the report also notes that the "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" (Advisory Council on the Misuse of Drugs (ACMD), 2013).

Information from seizures, collected samples and user websites suggest that 25I-NBOMe may have been 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.

⁽¹⁰⁾ Global Drug Survey 2013:
<http://www.globaldrugsurvey.com/global-drug-survey-2013>

Nevertheless, it also appears to be associated with the purchase of "research chemicals" or equivalent products via the Internet as well as products that are 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.

As noted, information from seizures and collected samples suggests that 25I-NBOMe is being sold directly on the illicit drug market as LSD. Consequently, populations using LSD may also be at risk of exposure to 25I-NBOMe. As such it may be relevant to consider the prevalence of LSD use. Among young adults (15- to 34-year-olds), lifetime prevalence of LSD use in Europe varies between countries, from 0.1 % to 5.4 % ⁽¹¹⁾. Last year use of LSD in this age group ranges from 0 % to 1.7 % ⁽¹²⁾. Last 30 days prevalence of LSD use in this age group ranges from 0 % to 0.6 % ⁽¹³⁾. Lifetime prevalence of LSD (or other hallucinogen use, excluding hallucinogenic mushrooms) among 15- to 16-year-old school students ranged from 1 % to 5 % in 25 Member States and Norway with ESPAD ⁽¹⁴⁾ surveys in 2011, with only the Czech Republic reporting a prevalence level of 5 %.

⁽¹¹⁾ For further details, including the countries reporting data, see:
<http://www.emcdda.europa.eu/stats13#display:/stats13/gpstab1c>

⁽¹²⁾ For further details, including the countries reporting data, see:
<http://www.emcdda.europa.eu/stats13#display:/stats13/gpstab2b>

⁽¹³⁾ For further details, including the countries reporting data, see:
<http://www.emcdda.europa.eu/stats13#display:/stats13/gpstab3b>

⁽¹⁴⁾ European school Survey Project on Alcohol and other Drugs.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

As mentioned in section A2, one animal study on conditioned fear extinction in mice currently exists where intraperitoneal administration of 25I-NBOMe (0.1, 0.3 and 1.0 mg/kg) led to decreased hippocampal neurogenesis (Catlow, et al., 2013). Halberstadt and Geyer confirmed that 25I-NBOMe significantly increased the head-twitch response rate in mice (0.1, 0.3, and 1 mg/kg) which was consistent with other serotonergic hallucinogens, thus, confirming mediation via 5-HT_{2A} receptors *in vivo* (Halberstadt and Geyer, 2014). However, there are currently no published studies regarding the acute toxicity of 25I-NBOMe in experimental animal models.

Recent research investigated the use of radiolabelled (¹⁵) 25I-NBOMe as a tool to study 5-HT_{2A} receptor density in animal brains by employing positron emission tomography imaging (Ettrup, et al., 2011, Ettrup, et al., 2010). Safety hazards and risks that are associated with the use of such radiolabelled compounds were not provided by the Member States. However it is possible that these are addressed under relevant national regulatory systems governing the use of radioactive materials.

D1.2. Human data

D1.2.1. User reports

No clinical trials were identified that have examined the subjective effects of 25I-NBOMe in humans; information is largely limited to that provided in case reports/series (see 'non-fatal intoxications', above) and self-reported experiences from user websites (Bluelight Forum, 2014, Drugs-Forum, 2014, Erowid, 2014b). Table 4 provides an overview of duration of effects when 25I-NBOMe is taken by the sublingual/buccal routes as well as when insufflated as reported by Erowid (2014c). Table 5 provides an overview of subjective effects of 25I-NBOMe as reported by Erowid (2014b). In both cases the information was collated from users, research, and other resources. No further details were provided on the methodology used to collate this information. Information provided in case reports and case series of non-fatal intoxications associated with 25I-NBOMe appear to support some of these reports. However, these need to be interpreted with caution as there was no analytical confirmation of the substances used. In addition, some of the users describe taking other drugs prior to or with 25I-NBOMe.

(¹⁵) Information on radiolabelled new psychoactive substances may be held by competent authorities at the national level. Such authorities may be able to provide essential information on the uses of such compounds which may be important in assessing their use.

Table 4. Examples of self-reported duration of effects of 25I-NBOMe per route of administration (tentative) as reported by Erowid (2014c). No information on the doses that were used was provided.

Duration of effects for 25I-NBOMe	Sublingual / Buccal	Insufflated
Total duration	6–10 hours	4–6 hours
Onset	15–120 minutes	5–10 minutes
Coming up	30–120 minutes	10–30 minutes
Plateau	120–240 minutes	60–120 minutes
Coming down	60–240 minutes	120–180 minutes
After effects	1–7 days	1–7 days

Table 5. Examples of subjective effects of 25I-NBOMe as reported by Erowid (2014b). No information on the doses that were used was provided.

Subjective effects of 25I-NBOMe

Positive	<ul style="list-style-type: none"> 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	<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, 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
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D1.2.2. 25I-NBOMe associated acute toxicity

Cases reported to the EU Early Warning System

A total of 32 non-fatal intoxications associated with 25I-NBOMe were reported by four Member States: Belgium, Poland, Sweden and the United Kingdom, and are detailed below. Fifteen of these cases have been analytically confirmed (Table 7) and it is worth noting that information content was limited to the information provided here. Toxicological investigations may still be ongoing and further updates may be available in due course.

Belgium

Belgium reported three non-fatal intoxications 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 but a pharmacokinetic study is being performed on the collected blood samples. The patients were admitted to the hospital, having consumed 'synthetic LSD' and clinical features included lowered consciousness, insufficient breathing, mydriasis, tachycardia, hypertension and 'lessened strength in four extremities'. The treatment was reported in two cases and 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 which occurred in August 2013. None of these cases were confirmed analytically. One of the patients reported that they had all used 25I-NBOMe.

Sweden

Sweden reported 18 non-fatal intoxications which occurred between June 2012 and July 2013. Five of these cases have been 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

The United Kingdom reported seven non-fatal intoxications where 25I-NBOMe was detected and which occurred over the course of one week (Hill, et al., 2013).

A summary of clinical features is shown in Table 6.

Table 6. Summary of clinical features in UK non-fatal cases reported by Hill et al. (2013).

Case no	1	2	3	4	5	6	7
Age	29	20	19	22	21	20	20
Sex	Male	Male	Male	Male	Male	Male	Male
Reported dose	nk	1 cap	'small amount'	nk	0.1 g	1 cap	1 cap
<u>Values on admission</u>							
Pulse (/min)	160	126	110	104	160	131	125
Blood pressure (mmHg)	187/171	170/90	138/100	118/58	150/80	132/67	154/90
Respiratory rate (/min)	58	24	15	18	15	19	19
O ₂ saturation (%)	94	92	96	97	98	98	98
Temperature (°C)	39.0	38.8	36.9	37.3	38.4	36.5	36.9
Glasgow coma scale	12	3	15	15	14	15	15
pH	7.20	7.30	7.48	7.33	nd	nd	nd
FiO ₂ (%) or L/Min of O ₂	0.7	15L	15L	0.21	nd	nd	nd
PaCO ₂ (kPa)	8.8	5.4	3.86	5.4	nd	nd	nd
PaO ₂ (kPa)	11.6	79.0	66.32	6.4	nd	nd	nd
Bicarbonate (mmol/L)	22	20	21	21	nd	nd	nd
Lactate (mmol/L)	2.1	4.06	0.9	6.1	3.7	nd	1.2
WBC (x 10 ⁹ /L)	23.5	8.5	18.9	7.0	11.1	7.3	10.5
Creatinine (umol/L)	140	79	87	77	79	82	74
ALT (IU/L)	121	nd	29	27	14	27	20
Creatine kinase (IU/L)	15424	228	326	633	598	100	92
<u>Clinical features at any time during admission</u>							
Pupillary dilatation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pyrexia (>38°C)	Yes	Yes	No	Yes	Yes	Yes	Yes
Agitation	Yes	Yes	Yes	Yes	Yes	No	No
Hallucinations	nk	Yes	Yes	Yes	Yes	Yes	Yes
Clonus	nk	Yes	No	No	nr	Yes	No
Seizures	Yes	Yes	No	Yes	No	No	No

Key: nk, not known; nr, not recorded; nd, not done; WBC, white blood cell count; ALT, alanine transaminase.

The first case described by Hill et al. (2013) 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. This case had the most severe clinical features reported by the United Kingdom including agitation, aggression, seizures, and 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 computer 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 an 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 although the extent to which these may have contributed to some of the effects related to psychostimulant-type toxidrome is unknown. 2C-I was also detected in all available urine samples (4 of the 7 cases) which suggests that 2C-I may be a metabolite of 25I-NBOMe. In three cases the capsules were swallowed and in the other three cases, the powder from the capsule was nasally insufflated. The quantities consumed are inexact, but were reported to range from 1 capsule (3 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 clinical features 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.

Case reports published in the literature from outside the European Union

United States of America

Case reports published in the medical literature from United States of America are summarised below. These include seven cases with analytical confirmation and fourteen cases without analytical confirmation.

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 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. (2014a) reported the presence of 25I-NBOMe in three emergency room patients. The patients presented with: 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. An earlier report described the detection of 25I-NBOMe in serum samples (250 and 2780 pg/mL) which were obtained from two "severely intoxicated" presentations at an emergency department and reference was made to a sympathomimetic toxidrome (tachycardia, hypertension, mydriasis, agitation and hypokalemia) plus hallucinations and bizarre behaviour (Poklis, et al., 2013).

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. 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.

An earlier publication by Rose et al. (2012) reported ten patients with an average age of 17 years (range 14 – 20 years) who presented to local EDs after ingestion and/or insufflation of a drug referred to be "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. Six patients were admitted to the ICU, two were treated in the ED and discharged, and one each was admitted to psychiatry or managed in a clinical decision unit and subsequently discharged. Three patients required intubation and ventilation, and all admitted patients were given intravenous benzodiazepines for sedation. All patients were discharged in good condition once symptoms resolved.

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 but had a normal blood pressure (as shown in the table below) and displayed varying levels of psychomotor agitation. None were capable of providing a clear history. Three patients experienced prolonged seizure activity which required pharmacological therapy, intubation, and mechanical ventilation. Patient D developed rhabdomyolysis and renal failure requiring haemodialysis.

	<u>Heart Rate</u>	<u>BP</u>	<u>Seizures?</u>	<u>Intubated?</u>	<u>Urine 25I (ng/mL)</u>	<u>Urine Others</u>
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

When reviewing the cases on published 25I-NBOMe intoxications, it was found that sympathomimetic features were commonly encountered: tachycardia (95%), agitation (77%), hallucinations (76%), hypertension (73%), and seizures (45%). In addition, it was noted that 25I-NBOMe intoxicated patients were observed to display persistent seizure activity, thus, resulting in rhabdomyolysis, requiring continuous administration of sedatives and skeletal muscle blocking agents, often for several days.

D1.2.3. 25I-NBOMe associated deaths

Cases reported to the EU Early Warning System

A total of four deaths associated with 25I-NBOMe were reported by three Member States: Belgium (2), Poland (1) and the United Kingdom (1). Only the death from the United Kingdom and one of the deaths from Belgium have been analytically confirmed (Table 7).

Belgium

Belgium reported one death which occurred in October 2013. The cause of death has 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. Further details are not available at present. Analytical confirmatory findings for 25I-NBOMe have not been reported.

In addition to the information provided in the Joint Report, Belgium reported a further death which occurred in November 2013 in Liège. A young man died after the consumption of 25I-NBOMe at home with friends. 25I-NBOMe was detected in the toxicological analysis. Death was attributed to natural causes.

Poland

Poland reported a death 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

The United Kingdom reported a death by drowning which occurred in May 2013 (Table 7). 25I-NBOMe was found on analysis of the post mortem blood of the deceased (insufficient sample volume for measurement as well as poor state of samples due to decomposition) as well as amphetamine, ketamine, lidocaine, 5-MeO-DiPT ⁽¹⁶⁾; DOI ⁽¹⁷⁾, 25C-NBOMe ⁽¹⁸⁾ and 2C-I (Soh and Elliott, 2013). Information had indicated that the deceased had possible access to 25I-NBOMe, 2C-E and possibly 25C-NBOMe and 2C-B.

Case reports published in the literature from outside the European Union

⁽¹⁶⁾ 5-Methoxy-diisopropyltryptamine

⁽¹⁷⁾ 2,5-Dimethoxy-4-iodoamphetamine

⁽¹⁸⁾ 2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine

Case reports published in the medical literature from non-European countries are summarised below. These include a total of seventeen analytically confirmed deaths in the United States of America and two non-analytically confirmed deaths in Australia.

United States of America

The Drug Enforcement Administration (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 up until July 2013 (DEA, 2013). 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.

Poklis et al. (2014b) reported a case of an accidental death (jumped or fallen from balcony) of a 19-year old male who appeared to display "bizarre" behaviour in the presence of friends. The postmortem results following analysis of several biofluids for 25I-NBOMe were as follows: peripheral blood 405 pg/mL, heart blood 410 pg/mL, urine 2.86 ng/mL, and vitreous humour 99 pg/mL, gastric contents 7.1 mg total, bile 10.9 ng/g, brain 2.54 ng/g, and liver 7.2 ng/g. Following arrest of the supplier, it was determined that the prepared dose of 25I-NBOMe per blotter paper thought to be in the region of 500 µg/section of blotter paper.

Australia

25I-NBOMe has been implicated in two 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) (19) (Caldicott et al., 2013). 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 (20). These cases have only been reported in the popular press and no further information or biological fluid analytical confirmation available for any of the cases.

(19) Telegraph Australia 2012 at <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>

(20) Telegraph Australia 2013 at: <http://www.dailytelegraph.com.au/newslocal/northern-beaches/police-warning-on-drug-that-killed-a-teenager-in-june/story-fngr8hax-1226765910968> and The Australian 2013 at: <http://www.theaustralian.com.au/news/nation/drug-link-to-sydney-teenagers-death-fall/story-e6frg6nf-1226658496485>.

Table 7. Analytically confirmed non-fatal and fatal intoxications associated with 25I-NBOMe and reported to the EU Early Warning System.

Country	Date of intoxication (gender, age)	Biological sample	25I-NBOMe result ⁽²¹⁾	Results for other substances ⁽²²⁾	Notes
Belgium	August 2013	Urine	+	None reported	Lowered consciousness, insufficient breathing, mydriasis, tachycardia (100/min)
Belgium	August 2013	Urine	+	None reported	Lowered consciousness, insufficient breathing, mydriasis, tachycardia (100/min)
Belgium	August 2013	Urine	+	None reported	Headache, lessened strength in 4 extremities, mydriasis, tachycardia (90/min), hypertension (150/85) Symptoms disappeared after being under observation for a couple of hours
Sweden	2012 – 2013	Not reported	+	None reported	25I-NBOMe detected in five non-fatal intoxications (no further details provided)
United Kingdom	January 2013 (M, 29)	Urine and plasma	+	2C-I, traces of amphetamine and methamphetamine	Severe clinical toxicity. Agitation, aggression, seizures, self-harming behaviour, tachycardia (160/min), hypertension (187/171), tachypnea, oxygen desaturation, pyrexia, rhabdomyolysis. Respiratory and metabolic acidosis, elevation of creatine kinase, impaired renal function. Anuria with a subsequent acute kidney injury. Acute respiratory distress syndrome Discharged from intensive care unit on day 38, released from hospital on day 43
United Kingdom	January 2013 (M, 20)	Urine and plasma	+	2C-I, traces of amphetamine and methamphetamine	Severe clinical toxicity. Convulsions (predominantly affecting face), high agitation, poor respiratory effort and clenched jaw. Tachycardia, hypertension, tachypnea, urinary retention, pupillary dilatation, pyrexia, elevated creatine kinase. Visual hallucinations Released from hospital on day 5

⁽²¹⁾ A "+" in this column indicates 25I-NBOMe was detected but no quantification was provided.

⁽²²⁾ 5-MeO-DIPT: 5-methoxy-diisopropyltryptamine; DOI: 2,5-dimethoxy-4-iodoamphetamine; 25C-NBOMe: 2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine

Country	Date of intoxication (gender, age)	Biological sample	25I-NBOMe result ⁽²¹⁾	Results for other substances ⁽²²⁾	Notes
United Kingdom	January 2013 (M, 20)	Urine and plasma	+	2C-I, traces of amphetamine and methamphetamine	Palpitations, visual hallucinations. Pupillary dilatation, 3 inducible beats of ankle clonus, sinus tachycardia Discharged on the day of admission
United Kingdom	January 2013 (M, 20)	Urine and plasma	+	2C-I, traces of amphetamine and methamphetamine	Palpitations, visual and auditory hallucinations. Tachycardia, pupillary dilatation Discharged on the day of admission
United Kingdom	January 2013 (M, 19)	Plasma	+	Traces of amphetamine and methamphetamine	Euphoria with visual and auditory hallucinations, violent and agitated behaviour Discharged after 15 h
United Kingdom	January 2013 (M, 22)	Plasma	+	Traces of amphetamine and methamphetamine	Nausea and visual hallucinations. Tonic-clonic seizure. Agitated and aggressive behaviour. Creatine kinase elevated Discharged on the day of admission
United Kingdom	January 2013 (M, 21)	Plasma	+	Traces of amphetamine and methamphetamine	Initial chaotic feeling followed by agitation, hallucinations and violent behaviour. Tachycardia and pyrexia Discharged after 15 h

Country	Date of intoxication (gender, age)	Biological sample	25I-NBOMe result ⁽²¹⁾	Results for other substances ⁽²²⁾	Notes
Belgium	November 2013 (M, not reported)	Not reported	+	None reported	Fatal intoxication Cause of death: natural
United Kingdom	May 2013 (M, 22)	Blood (post-mortem)	+	Amphetamine, ketamine, lidocaine, 5-MeO-DiPT, DOI, 25C-NBOMe and 2C-I	Fatal intoxication Cause of death: drowning

16. A "+" in this column indicates 25I-NBOMe was detected but no quantification was provided.

17. 5-MeO-DIPT: 5-methoxy-diisopropyltryptamine; DOI: 2,5-dimethoxy-4-iodoamphetamine; 25C-NBOMe: 2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine.

D2. Chronic health effects

D2.1. Animal data

There are no published studies investigating the chronic health effects of 25I-NBOMe in animals.

D2.2. Human data

There are no published studies investigating the chronic health effects of 25I-NBOMe in humans.

D3. Factors affecting public health risks

D3.1. Availability and quality of the new psychoactive substance on the market

25I-NBOMe is offered for sale by Internet retailers as a substance in its own right and it appears that Internet vendors may form the key source of supply. A search of google.com using the search string 'buy "25I-NBOMe"' conducted by the EMCDDA in December 2013 for the Joint Report identified a number of online shops offering 25I-NBOMe for sale in both retail and wholesale quantities. In the former case 25I-NBOMe may be sold as a "research chemical". In addition, NBOMe products (including 25I-NBOMe) have been reported to be obtained from "street dealers", including at festivals.

Data from the (Australian) National Drug and Alcohol Research Centre's deep web monitoring programme of the Silk Road marketplace (23,24) (Christin, 2012) identified 29 retailers in early February 2013 offering compounds from the "NBOMe family" for sale (Van Buskirk et al., 2013). Details of the specific compounds offered, quantities, dosage forms, and prices were not provided. The number of such retailers was relatively stable over the preceding four months of monitoring (25). It is important to note that the study was conducted before Silk Road was seized and taken offline in October 2013 by the United States Federal Bureau of Investigation. No studies were identified that have examined the sale of 'NBOMe' compounds, including 25I-NBOMe, since then.

Seizure data as well as information from collected samples reported by the Member States suggests that 25I-NBOMe is sold as a drug in its own right and directly on the illicit drug market as LSD. No information was reported on the price of 25I-NBOMe when sold as LSD.

Overall, whilst some individuals may be exposed to 25I-NBOMe intentionally, others may be exposed unintentionally after consuming a product with no indication that it contains this substance or following its ingestion as a component of a mixture of other active substances (section C). In cases where 25I-NBOMe is available in a blotter formulation, one might expect to find certain limits with regards to drug concentration and combination inherent in this dosage form. However, detailed information about this is not available.

⁽²³⁾ The National Drug and Alcohol Research Centre (NDARC) is based at the University of New South Wales, Sydney, Australia

⁽²⁴⁾ Silk Road is an anonymous, international online marketplace that operates as a Tor hidden service. It uses the peer-to-peer payment network and digital currency Bitcoin for monetary transactions. The original Silk Road marketplace was seized and taken offline on 2 October 2013 by the United States Federal Bureau of Investigation. Since then a new version of Silk Road, sometimes described as 'Silk Road 2.0', has become operational.

⁽²⁵⁾ 29 retailers were identified in late October 2012; 33 in mid-November 2012; 27 in late November 2012; 29 in mid-December 2012; 24 in early January 2013; 24 in mid-January 2013.

D3.2. Availability of the information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects

As of 9th March 2014, the Erowid website hosts seventy-eight experience reports that describe the effects and potential health / adverse effects related to the use of 25I-NBOMe and it appears that both dose and dosage form (e.g. blotters vs. insufflation of powder) may have an impact on the psychoactive effects (Erowid, 2014b). Given its high potency, and the potential to overdose, there is some indication that nasal insufflation may be discouraged as an example to provide harm reduction advice (Erowid, 2014a).

D3.3. Characteristics and behaviour of users

There are self-reports from users on Internet drug discussion forums who believe that they have specifically taken 25I-NBOMe although no studies were identified that examined the characteristics of users of 25I-NBOMe. It is important to note that it is not possible to confirm the specific substance(s) used, nor the purity, dose, etc. Analysis of products containing new psychoactive substances that are sold on the drug market have shown that the composition can differ between that claimed by the retailer, as well as differ over different geographical areas and time. Similar caveats apply to these types of information that have been provided in case reports/series unless biological and collected samples were taken and subjected to toxicological and forensic analysis. In addition, the information provided by patients in case reports/series as well as that provided on user websites should be regarded as illustrative only and not taken as representative of users of 25I-NBOMe in general. Finally, information from seizures, collected samples and user websites suggest that 25I-NBOMe has been commonly sold as a 'legal' replacement for LSD (26) or sold as LSD directly on the illicit drug market. In the latter case users may be unaware that they are using 25I-NBOMe. Additional research is required in order to examine to what extent the characteristics of 25I-NBOMe users overlap and/or reflect those who use LSD.

D3.4. Nature and extent of health consequence

The documented information on the acute health effects of 25I-NBOMe have been discussed in section D1.2. The United Kingdom reported the detection of 25I-NBOMe in an intoxicated driver.

D3.5. Long-term consequences of use

As discussed in sections D2.1. and D2.2. there are no animal or human data on the chronic health effects of 25I-NBOMe. In particular, there have been no long-term follow up studies to determine whether 25I-NBOMe users are at greater risk of health deterioration later in life, or of developing chronic or life-threatening medical conditions.

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

⁽²⁶⁾ For example use of the street names 'legal acid' and 'Hoffman'.

As noted, it appears that the sourcing and use of 25I-NBOMe is generally related to individuals attempting to source the drug itself from online sources. It is likely that 25I-NBOMe is used in the same environments as other hallucinogens. This would be typically (but not restricted to) home environments, discotheques/nightclubs and outdoor music festivals.

Section E. Social Risks

E1. Individual social risks

There are currently no data to be able to determine the impact of 25I-NBOMe in this area.

E2. Possible effects on direct social environment

There are currently no data to be able to determine the impact of 25I-NBOMe in this area.

E3. Possible effects on society as a whole

There are currently no data to be able to determine the impact of 25I-NBOMe in this area. The United Kingdom reported the detection of 25I-NBOMe in biological samples of two criminal suspects in a drug-related death and an intoxicated driver. No further details are available.

E4. Economic costs

It is currently not possible to estimate the healthcare costs associated with 25I-NBOMe.

E5. Possible effects related to the cultural context, for example marginalisation

There are currently no data to be able to determine the impact of 25I-NBOMe in this area.

E6. Possible appeal of the new psychoactive substance to specific population groups within the general population

There are currently no data to be able to determine the possible appeal of 25I-NBOMe to specific population groups within the general population.

Section F. Involvement of organised crime

F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain

Germany reported that no links have been identified between organised crime groups and the production, trafficking and/or distribution of 25I-NBOMe. They also noted that it should be borne in mind that given the easy access to substances (which can be in large amounts)

via Internet retailers it cannot be excluded that a certain level of organisation may exist. In addition, the interest and presence of organised crime groups in the phenomenon of new psychoactive substances can be easily concluded from the substantial profits that can be obtained from this type of activity.

F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances

Based on the information available to ECMDDA and Europol it does not appear that the production, trafficking and distribution of 25I-NBOMe impacts on other existing psychoactive substances or new psychoactive substances.

F3. Evidence of the same groups of people being involved in different types of crime

No information has been received by Europol of evidence of the same groups of people being involved in different types of crime in connection with 25I-NBOMe.

F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)

No information has been received by Europol on incidents of violence in connection with 25I-NBOMe.

F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society

No information has been received by Europol on incidents of money-laundering or impact of organised crime on other socioeconomic factors in society in connection with 25I-NBOMe.

F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)

There are currently no data to be able to determine the impact of 25I-NBOMe in this area.

F7. Use of violence between or within criminal groups

No information has been received by Europol on incidents of violence in connection with 25I-NBOMe.

F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation

No information has been received by Europol on strategies to prevent prosecution in connection with 25I-NBOMe.

References

Abdel-Magid, A. F., Carson, K. G., Harris, B. D., Maryanoff, C. A. and Shah, R. D. (1996), 'Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures', *Journal of Organic Chemistry*, 61(11), pp. 3849-3862.

Advisory Council on the Misuse of Drugs (ACMD) (2013), 'NBOMe compounds: a review of the evidence of use and harm', Available at: <https://www.gov.uk/government/publications/nbome-compounds-a-review-of-the-evidence-of-use-and-harm> (March 2014).

Baxter, E. W. and Reitz, A. B. (2002). *Reductive aminations of carbonyl compounds with borohydride and borane reducing agents*, John Wiley & Sons, Inc., New York.

Bluelight Forum (2014), 'The big & dandy 25I-NBOMe thread', Available at: <http://www.bluelight.org/vb/threads/551797-The-Big-amp-Dandy-551725I-NBOMe-Thread> (March 552014).

Boyer, E. W. and Shannon, M. (2005), 'The serotonin syndrome', *New England Journal of Medicine*, 352(11), pp. 1112-1120.

Braden, M. R. (2007), 'Towards a biophysical understanding of hallucinogen action', Ph.D. dissertation, Purdue University, USA.

Braden, M. R., Parrish, J. C., Naylor, J. C. and Nichols, D. E. (2006), 'Molecular interaction of serotonin 5-HT_{2A} receptor residues Phe339(6.51) and Phe340(6.52) with superpotent N-benzyl phenethylamine agonists', *Molecular Pharmacology*, 70(6), pp. 1956-1964.

Brandt, S. D. (2014), 'Shulgin's 2C & 3C series: prototypes for hallucinogen research. Translation to NBOMe analogs', American Academy of Forensic Sciences (AAFS) Workshop #18 - "Novel Psychoactive Substances (NPS): Pharmacology, Toxicology, Psychiatry and Case Reports". AAFS 66th Annual Scientific Meeting, Seattle, 18 February.

Caldicott, D. G., Bright, S. J. and Barratt, M. J. (2013), 'NBOMe - a very different kettle of fish...' *Medical Journal of Australia*, 199(5), pp. 322-323.

Canal, C. E. and Morgan, D. (2012), 'Head-twitch response in rodents induced by the hallucinogen 2,5-dimethoxy-4-iodoamphetamine: a comprehensive history, a re-evaluation of mechanisms, and its utility as a model', *Drug Testing and Analysis*, 4(7-8), pp. 556-576.

Casale, J. F. and Hays, P. A. (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 Journal*, 9(2), pp. 84-109.

Catlow, B. J., Song, S., Paredes, D. A., Kirstein, C. L. and Sanchez-Ramos, J. (2013), 'Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning', *Experimental Brain Research*, 228(4), pp. 481-491.

Christin, N. (2012), 'Traveling the Silk Road: a measurement analysis of a large anonymous online marketplace', Available at: <http://www.andrew.cmu.edu/user/nicolasc/publications/TR-CMU-CyLab-12-018.pdf> (March 2014).

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', Available at: <http://www.regulations.gov/contentStreamer?objectId=090000648147faf090000648149&disposition=attachment&contentType=pdf> (March 090000642014).

<http://www.regulations.gov/#!documentDetail;D=DEA-2013-0011-0001> (March 2014)

Drugs-Forum (2014), '25I-NBOMe', Available at: <http://www.drugs-forum.com/forum/showwiki.php?title=25I-NBOMe> (March 2014).

EMCDDA–Europol (2014), 'EMCDDA–Europol Joint Report on a new psychoactive substance: 25I-NBOMe (4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine). Available at: <http://www.emcdda.europa.eu/publications/joint-report/25I-NBOMe> (March 2014)', EMCDDA, Lisbon.

EMCDDA (2004), 'Report on the risk assessment of 2C-I, 2C-T-2 and 2C-T-7 in the framework of the joint action on new synthetic drugs', EMCDDA, Lisbon, May 2004. Available at: <http://www.emcdda.europa.eu/html.cfm/index33353EN.html> (March 32014).

EMCDDA (2013), '25B-N(BOMe)2', Early-warning-system on new drugs (2013). European Monitoring Centre for Drugs and Drug Addiction Database on New Drugs (EDND).

Erowid (2014a), '25I-NBOMe', Available at: http://www.erowid.org/chemicals/2ci_nbome (March 2014).

Erowid (2014b), '2C-I-NBOMe reports', Available at:
http://www.erowid.org/experiences/subs/exp_2CINBOMe.shtml (March 2014).

Erowid (2014c), '25I-NBOMe (2C-I-NBOMe). Effects.' Available at:
http://www.erowid.org/chemicals/2ci_nbome/2ci_nbome_effects.shtml (March 2014).

Ettrup, A., Hansen, M., Santini, M. A., Paine, J., Gillings, N., Palner, M., Lehel, S., Herth, M. M., Madsen, J., Kristensen, J., Begtrup, M. and Knudsen, G. M. (2011), 'Radiosynthesis and in vivo evaluation of a series of substituted ¹¹C-phenethylamines as 5-HT_{2A} agonist PET tracers', *European Journal of Nuclear Medicine and Molecular Imaging*, 38(4), pp. 681-693.

Ettrup, A., Palner, M., Gillings, N., Santini, M. A., Hansen, M., Kornum, B. R., Rasmussen, L. K., Någren, K., Madsen, J., Begtrup, M. and Knudsen, G. M. (2010), 'Radiosynthesis and evaluation of ¹¹C-CIMBI-5 as a 5-HT_{2A} receptor agonist radioligand for PET', *Journal of Nuclear Medicine*, 51(11), pp. 1763-1770.

Geyer, M. A. and Vollenweider, F. X. (2008), 'Serotonin research: contributions to understanding psychoses', *Trends in Pharmacological Sciences*, 29(9), pp. 445-453.

Gillings, N. (2009), 'A restricted access material for rapid analysis of [¹¹C]-labeled radiopharmaceuticals and their metabolites in plasma', *Nuclear Medicine and Biology*, 36(8), pp. 961-965.

Glennon, R. A., Dukat, M., El-Bermawy, M., Law, H., De Los Angeles, J., Teitler, M., King, A. and Herrick-Davis, K. (1994), 'Influence of amine substituents on 5-HT_{2A} versus 5-HT_{2C} binding of phenylalkyl- and indolylalkylamines', *Journal of Medicinal Chemistry*, 37(13), pp. 1929-1935.

González-Maeso, J. and Sealfon, S. C. (2009), 'Psychedelics and schizophrenia', *Trends in Neurosciences*, 32(4), pp. 225-232.

Halberstadt, A. L. and Geyer, M. A. (2013), 'Serotonergic hallucinogens as translational models relevant to schizophrenia', *International Journal of Neuropsychopharmacology*, 16(10), pp. 2165-2180.

Halberstadt, A. L. and Geyer, M. A. (2014), 'Effects of the hallucinogen 2,5-dimethoxy-4-iodophenethylamine (2C-I) and superpotent N-benzyl derivatives on the head twitch response', *Neuropharmacology*, 77(0), pp. 200-207.

Halberstadt, A. L. and Nichols, D. E. (2010). Serotonin and serotonin receptors in hallucinogen action, In: *Handbook of the behavioral neurobiology of serotonin*, eds. Müller,

C.P., Jacobs, B.L., Academic Press, London, pp. 621-636.

Hanks, J. B. and González-Maeso, J. (2013), 'Animal models of serotonergic psychedelics', *ACS Chemical Neuroscience*, 4(1), pp. 33-42.

Hansen, M. (2010), 'Design and synthesis of selective serotonin receptor agonists for positron emission tomography imaging of the brain', Ph.D. dissertation, University of Copenhagen, Denmark.

Hansen, M., Phonekeo, K., Paine, J. S., Leth-Petersen, S., Begtrup, M., Bräuner-Osborne, H. and Kristensen, J. L. (2014), 'Synthesis and structure-activity relationships of N-benzyl phenethylamines as 5-HT_{2A/2C} agonists', *ACS Chemical Neuroscience*, in press; 10.1021/cn400216u.

Heim, R. (2003), 'Synthese und Pharmakologie potenter 5-HT_{2A}-Rezeptoragonisten mit N-2-Methoxybenzyl-Partialstruktur. Entwicklung eines neuen Struktur-Wirkungskonzepts', Ph.D. dissertation, Freie Universität Berlin, Germany.

Heim, R. and Elz, S. (2000), 'Novel extremely potent partial 5-HT_{2A}-receptor agonists: successful application of a new structure-activity concept', *Arch. Pharm. Pharm. Med Chem.*, 333(Suppl. 1), pp. 18 (39).

Hill, S. L., Doris, T., Gurung, S., Katebe, S., Lomas, A., Dunn, M., Blain, P. and Thomas, S. H. L. (2013), 'Severe clinical toxicity associated with analytically confirmed recreational use of 25I-NBOMe: case series', *Clinical Toxicology*, 51(6), pp. 487-492.

Isbister, G. K., Buckley, N. A. and Whyte, I. M. (2007), 'Serotonin toxicity: a practical approach to diagnosis and treatment', *Medical Journal of Australia*, 187(6), pp. 361-365.

Kelly, A., Eisenga, B., Riley, B. and Judge, B. (2012), 'Case series of 25I-NBOMe exposures with laboratory confirmation', *Clinical Toxicology*, 50(7), pp. 702-702.

Lawn, W., Barratt, M., Williams, M., Horne, A. and Winstock, A. (2014), 'The NBOMe hallucinogenic drug series: Patterns of use, characteristics of users and self-reported effects in a large international sample', *Journal of Psychopharmacology*, in press; doi: 10.1177/0269881114523866

Leth-Petersen, S., Bundgaard, C., Hansen, M., Carnerup, M. A., Kehler, J. and Kristensen, J. L. (2014), 'Correlating the metabolic stability of psychedelic 5-HT agonists with anecdotal reports of human oral bioavailability', *Neurochemical Research*, in press; doi: 10.1007/s11064-11014-11253-y.

Nichols, D. E. (2004), 'Hallucinogens', *Pharmacology & Therapeutics*, 101(2), pp. 131-181.

Nichols, D. E. (2012), 'Structure-activity relationships of serotonin 5-HT_{2A} agonists', *WIREs Membrane Transport and Signaling*, 1(5), pp. 559-579.

Nichols, D. E., Frescas, S. P., Chemel, B. R., Rehder, K. S., Zhong, D. and Lewin, A. H. (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(11), pp. 6116-6123.

NIMH-PDSP 'National Institute of Mental Health's Psychoactive Drug Screening Program', University of North Carolina at Chapel Hill. Available at: <http://pdsp.med.unc.edu/indexR.html> (March 2014).

Poklis, J. L., Charles, J., Wolf, C. E. and Poklis, A. (2013), 'High-performance liquid chromatography tandem mass spectrometry method for the determination of 2CC-NBOMe and 25I-NBOMe in human serum', *Biomedical Chromatography*, 27(12), pp. 1794-1800.

Poklis, J. L., Clay, D. J. and Poklis, A. (2014a), 'High-performance liquid chromatography with tandem mass spectrometry for the determination of nine hallucinogenic 25-NBOMe designer drugs in urine specimens', *Journal of Analytical Toxicology*, in press; doi:10.1093/jat/bku1005.

Poklis, J. L., Devers, K. G., Arbefeville, E. F., Pearson, J. M., Houston, E. and Poklis, A. (2014b), '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*, 234(e14-e20).

Rose, R. S., Cumpston, K. L., Stromberg, P. E. and Wills, B. K. (2012), 'Severe poisoning following self-reported use of 25-I, a novel substituted amphetamine', *Clinical Toxicology*, 50(7), pp. 707-708.

Rose, S. R., Poklis, J. L. and Poklis, A. (2013), 'A case of 25I-NBOMe (25-I) intoxication: a new potent 5-HT_{2A} agonist designer drug', *Clinical Toxicology*, 51(3), pp. 174-177.

Soh, Y. N. and Elliott, S. (2013), 'An investigation of the stability of emerging new psychoactive substances', *Drug Test Anal*, in press; doi: 10.1002/dta.1576.

Stellpflug, S. J., Kealey, S. E., Hegarty, C. B. and Janis, G. C. (2013), '2-(4-Iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe): clinical case with

unique confirmatory testing', *Journal of Medical Toxicology*, in press; doi 10.1007/s13181-13013-10314-y.

Sternbach, H. (1991), 'The serotonin syndrome', *American Journal of Psychiatry*, 148(6), pp. 705-713.

Van Buskirk, J., Roxburgh, A., Bruno, R. and Burns, L. (2013), 'Drugs and the Internet', Issue 1, August 2013. Sydney: National Drug and Alcohol Research Centre. Available at: http://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/DrugsTheInternet_Newsletter%20FINAL%20with%20ISSN.pdf (March 2014).

Walterscheid, J. P., Phillips, G. T., Lopez, A. E., Gonsoulin, M. L., Chen, H. H. and Sanchez, L. A. (2014), 'Pathological findings in 2 cases of fatal 25I-NBOMe toxicity', *The American Journal of Forensic Medicine and Pathology*, 35(1), pp. 20-25.