European Monitoring Centre
for Drugs and Drug Addiction

EUROPOL

EMCDDA–Europol Joint Report on a new psychoactive substance: 25I-NBOMe (4-iodo-2,5-dimethoxy-*N*-(2-methoxybenzyl)phenethylamine)

In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

Contents

1. Introduction

Article 5.1 of Council Decision 2005/387/JHA ([1]) (hereinafter referred to as the 'Decision') stipulates that *'Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report (hereinafter the 'Joint Report').*' The Joint Report shall be submitted to the Council, the European Medicines Agency (EMA) and the European Commission.

At the end of September 2013, the EMCDDA and Europol examined the available information on a new psychoactive substance 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine, commonly known by the abbreviation '25I-NBOMe', through a joint assessment based upon the following criteria:

1. the amount of the material seized;
2. evidence of organised crime involvement;
3. evidence of international trafficking;
4. analogy with better-studied compounds;
5. evidence of the potential for further (rapid) spread; and,
6. evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information collected on 25I-NBOMe satisfied criteria 1, 3, 5 and 6. The two organisations therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on 25I-NBOMe as stipulated by Article 5.1 of the Decision.

2. Information collection process

In compliance with the provisions of the Decision, on 7 October 2013 the EMCDDA and Europol launched a procedure for the collection of information on 25I-NBOMe, in order to prepare the Joint Report. The information was collected mainly through the Reitox National Focal Points in the Member States, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway and Iceland. The information collection process was largely concluded by 18 November 2013; additional

([1]) OJ L 127, 20.5.2005, p. 32.

information and clarifications from some countries were received up to four weeks after this date.

Europol asked the Europol National Units to provide information on:

- the level of production of 25I-NBOMe in their country;
- the level of distribution of 25I-NBOMe in their country;
- the level of trafficking of 25I-NBOMe in their country, both for internal, transit or export purposes;
- the number of seizures of 25I-NBOMe in their country, the total amount of the seizures, country of origin, details on the physical forms (including photos);
- the role of organised crime, or criminal groups, in the production, distribution and trafficking of 25I-NBOMe in their country; and,
- any known aspect of violence and/or money laundering relating to the production and trafficking of 25I-NBOMe.

Europol received responses from 15 Member States.

According to Article 5.3 of the Decision, the EMA requested the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway and Iceland provide information on whether:

- the new psychoactive substance 25I-NBOMe has obtained a marketing authorisation;
- the new psychoactive substance 25I-NBOMe is the subject of an application for a marketing authorisation; and,
- a marketing authorisation that had been granted in respect of the new psychoactive substance 25I-NBOMe has been suspended.

Twenty-four Member States ([2]), Norway and Iceland responded to the EMA's request. The EMA also provided information as relevant to the central authorisation procedure.

Furthermore, in anticipation of Article 7.3 of the Decision in relation to the manufacturing of medicinal products in the European Union, the EMA also requested whether the new psychoactive substance 25I-NBOMe is used to manufacture a medicinal product:

- which has been granted a marketing authorisation;

([2]) Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

- for which an application has been made for a marketing authorisation; and,
- for which a marketing authorisation has been suspended by a competent authority.

Twenty-three Member States ([3]), Norway and Iceland replied to the EMA's request. The EMA also provided information as relevant to the central authorisation procedure.

The EMCDDA collected data through:

1. a structured questionnaire from the Reitox National Focal Points. The EMCDDA received replies from 28 Member States as well as from Turkey and Norway;

2. data previously provided to the EU Early Warning System via EMCDDA-Europol Reporting Forms, EWS Progress and Final Reports;

3. a specific information request to the World Health Organization on whether or not methoxetamine is under assessment by the United Nations system (see section 3.5), and;

4. a structured search of the scientific literature and of relevant Internet sites.

Thus, information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part). The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. The conclusion of the Joint Report was prepared and agreed by the two organisations responsible — the EMCDDA and Europol. Further details of the seizures and collected samples (including images where available) reported to the EMCDDA are provided in Annex 1. The details of non-fatal intoxications and a death associated with 25I-NBOMe that have been reported to the EMCDDA are provided in Annex 2.

3. Information required by Article 5.2 of the Decision

The order and titles of subsections 3.1 to 3.8 and section 4 below are as they appear in Article 5.2(a) to (h) and Article 5.3(a) to (c) of the Decision; all sections are cross-referenced with those set down in the Decision.

([3]) Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

3.1 Chemical and physical description, including the names under which the new psychoactive substance is known — Article 5.2(a) of the Decision

Chemical description and names

25I-NBOMe is a derivative of 2C-I (4-iodo-2,5-dimethoxyphenethylamine), a known synthetic derivative of phenethylamine with stimulant and hallucinogenic properties. 2C-I was the subject of a risk assessment at European level in 2003 (EMCDDA, 2004). 25I-NBOMe contains the 2C-I substructure, substituted with a bulky '*N*-(2-methoxy)benzyl' group. The 'I' in 2C-I and 25I-NBOMe denotes the presence of an iodine atom in the structure (Figure 1).

Several similar versions of 25I-NBOMe exist where the iodine atom is exchanged for another halide element, hydrogen atom or organic functional group, i.e. bromine (25B-NBOMe), chlorine (25C-NBOMe), hydrogen atom (25H-NBOMe), -methyl (25D-NBOMe), -ethyl (25E-NBOMe), -nitro (25N-NBOMe) or –isopropyl (25iP-NBOMe). These compounds are informally called the 'NBOMes'. This name comes from the '**N**-**b**enzylmethoxy' substituent (-methoxy being written in chemical shorthand as '**OMe**'). As of 12 December 2013, ten '-NBOMe' compounds have been notified to the EU early warning system and it is important to note that –NBOMe compounds can be derived from all '2C' phenethylamines. Furthermore, two simple variants of 25I-NBOMe are possible by moving the methoxy group, found in position -2 on the benzyl moiety, to position -3 or -4. Furthermore, many other chemical variants are possible by changing the substitution pattern on the benzyl moiety to produce substances, the effects of which may or may not be similar to 25I-NBOMe.

The IUPAC name for 25I-NBOMe is: 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine.

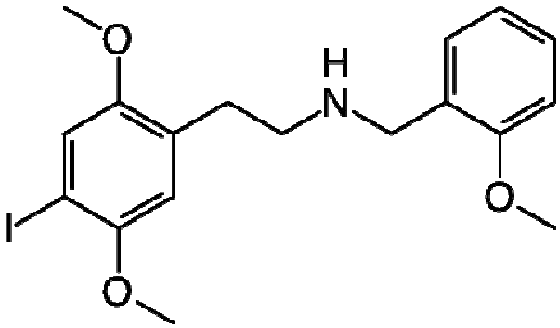
Additional chemical synonyms have been reported:

2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine;
2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethan-1-amine;
4-iodo-2,5-dimethoxy-*N*-(2-methoxybenzyl)phenethylamine;
4-iodo-2,5-dimethoxy-*N*-(o-methoxybenzyl)phenethylamine;
4-jodo-2,5-dimetoksi-*N*-(2-metoksibentsyyli)fenetyyliamiini (Finnish);
4-iodo-2,5-dimethoxy-*N*-[(2-methoxyphenyl)methyl]-benzeneethanamine;
N-(2-methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine; and,
N-(2-methoxybenzyl)-4-iodo-2,5-dimethoxyphenethylamine.

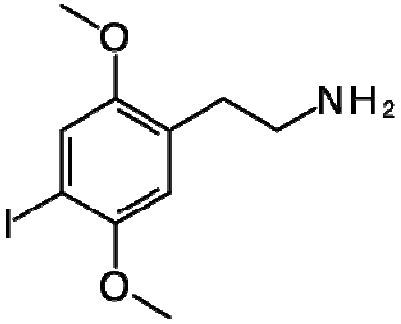
Furthermore, common names or codenames have also been reported: 25I, 2CI-NBOMe or 2C-I-NBOMe, NBOMe-2C-I or NBOMe-2CI, BOM-CI, Cimbi-5, Solaris and INBMeO.

Finally, the following street names have been reported: '25I', 'dots', 'legal acid', 'N-Bomb', 'NE-BOME', 'smiles', 'INBMeO', 'BOM-CI', 'Hoffman' and 'N-boom'.

Figure 1. The numbered molecular structure, formula, weight and monoisotopic mass of 25I-NBOMe. The molecular structure for 2C-I is provided for comparison.



25I-NBOMe



2C-I

Molecular formula: $C_{18}H_{22}INO_3$

Molecular weight: 427.2767

Monoisotopic mass: 427.064

Chemical Abstract Service registry numbers (CAS RN)

919797-19-6 free base
1043868-97-8 hydrochloride salt
1248338-50-2 ^{11}C radiolabelled base – ^{11}C on the benzyl methoxy carbon
1404305-56-1 ^{11}C radiolabelled base – ^{11}C on the phenyl 2-methoxy carbon
1043869-41-5 ^{3}H radiolabelled base

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS registry numbers listed above. The search returned no results.

Physical description

The hydrochloride salt form of 25I-NBOMe is a crystalline solid at room temperature. It has been reported that some Internet retailers ([4]) have advertised 25I-NBOMe as the free base and also as a hydroxypropyl-*β*-cyclodextrin (HPBCD) complex. In both

([4]) 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'.

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.

A more detailed description of 25I-NBOMe seizures and collected samples encountered can be found in subsections 3.2.1 and 3.2.2 below.

3.2 Information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance — Article 5.2(b) of the Decision

3.2.1 Information provided to Europol

Europol received replies from 15 Member States (Belgium, Bulgaria, Croatia, Cyprus, Estonia, Finland, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Poland, Slovakia and Slovenia). Of these, nine countries had no data relating to 25I-NBOMe (Bulgaria, Croatia, Cyprus, Estonia, Italy, Latvia, Lithuania, Luxembourg and Slovenia). The remaining six countries (Belgium, Finland, Germany, Hungary, Poland and Slovakia) reported the following information.

The level of production, distribution and trafficking

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).

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.

3.2.2 Information provided to the EMCDDA

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 reported detections of 25I-NBOMe ([5]).

Seizures

Twenty-two Member States (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 reported seizures of 25I-NBOMe.

25I-NBOMe has typically been seized as ‘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).

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, 2C-C-NBOMe, 2C-I-NBOMe, 2C-H-NBOMe), 2C-B, 2C-C, 2C-I, 2C-T-4, mescaline ([6]), LSD, MDPBP (a synthetic cathinone) and an unknown substance. No quantitative analyses were available.

([5]) ‘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.)

([6]) A naturally occurring hallucinogenic phenethylamine.

There is some evidence that 25I-NBOMe has been sold as a replacement for the internationally controlled hallucinogenic substance LSD (lysergic acid diethylamide) which is also commonly taken sublingually in the form of blotters. 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.). Many of these designs have been associated with LSD in the past. 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 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 one death 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 section 3.4.1 and Annex 2.

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 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 Annex 1.

3.3 Information on the involvement of organised crime in the manufacture or trafficking of the new psychoactive substance — Article 5.2(c) of the Decision

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.

Money laundering aspects

No information was received on money laundering connected to the production and/or trafficking of 25I-NBOMe.

Violence in connection with production, wholesale and distribution

No information was received on incidents of violence in connection with the production, wholesale and/or trafficking of 25I-NBOMe.

3.4 A first indication of the risks associated with the new psychoactive substance, including the health and social risks, and of the characteristics of users — Article 5.2(d) of the Decision

3.4.1 First indication of health risks

A total of 32 non-fatal intoxications and three deaths associated with 25I-NBOMe were reported by four Member States: Belgium, Poland, Sweden and the United Kingdom. Not all of these cases have been analytically confirmed. See Annex 2 for further details on toxicologically confirmed cases.

Non-fatal intoxications

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 symptoms included lowered consciousness, insufficient breathing, mydriasis, tachycardia, hypertension and ‘lessened strength in four extremities’ (see the details for all patients in Annex 2). 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 they all had 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).

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 symptoms 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 computed tomography (CT) scan revealed mild cerebral oedema but no other intracranial pathology. Treatment consisted of initial resuscitation with intubation, ventilation, intravenous sedation, antibiotics and fluids. Ongoing jerking seizure-like movements were noted and managed with atracurium infusion. Large doses of multi-modal sedation were administered during stabilisation. On day 18 of treatment a percutaneous tracheostomy was performed. The patient was discharged from intensive care on day 38, and discharged from hospital on day 43.

In the other six cases, 25I-NBOMe had been taken at a house party after it had been purchased from the Internet. The 25I-NBOMe was in the form of powder contained in purple capsules, labelled as ‘2C-B’. The six cases were analytically confirmed either

in plasma alone or in urine and plasma. Amphetamine and methamphetamine were detected together with 25I-NBOMe in all six patients. 2C-I ([7]) was also detected in all available urine samples (4 of the 7 cases); this may suggest that 2C-I is 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 symptomatology varied slightly between patients. One of these patients suffered severe toxicity, which required hospitalisation for 5 days (see the details of symptoms for all patients in Annex 2). 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.

Deaths

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. The results of the analytical confirmation on biological samples are awaited.

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 expected.

United Kingdom

The United Kingdom reported a death by drowning which occurred in May 2013. 25I-NBOMe was found on analysis of the post mortem blood of the deceased as well as

([7]) 2,5-Dimethoxy-4-iodophenethylamine

amphetamine, ketamine, lignocaine, 5-MeO-DiPT ([8]); DOI ([9]), 25C-NBOMe ([10]) and 2C-I ([7]). No further information is available.

Pharmacology and mode of action

Data from *in vitro* studies has shown that 25I-NBOMe has nanomolar affinity for the serotonin 5-HT_{2A} receptor and is a full agonist (Braden et al, 2006; Ettrup et al., 2010; Ettrup et al., 2011; Nichols et al., 2008). The addition of the 2-methoxybenzyl group significantly enhances the affinity and potency of 25I-NBOMe (Braden et al, 2006) compared to 2C-I (Blaazer et al., 2008).

Stimulation of the 5-HT_{2A} receptors appears to be essential for the hallucinogenic effects of drugs such as LSD (Egan et al. 1998, Marek & Aghaajanian, 1996; González-Maeso et al., 2007; Hanks & González-Maeso, 2013; Nelson et al., 1998). Given the fact that 25I-NBOMe is a potent full agonist for the 5-HT_{2A} receptor and there have been reports of its hallucinogenic effects when used as a recreational drug, Halberstadt and Geyer (2013) studied the effect of 25I-NBOMe on the head-twitch behavioural response (HTR) in mice which is used as a surrogate marker of the hallucinogenic effect of 5-HT_{2A} receptor activation in humans (Hanks & González-Maeso, 2013). The study found that 25I-NBOMe induces HTR in mice in a dose-dependent manner, with a dose of 0.01 mg/kg s.c. inducing significant HTR compared to controls. HTR was dose-dependently antagonised by pre-treatment of the mice with the 5-HT_{2A} receptor antagonist M100,907 suggesting that the HTR induced by 25I-NBOMe is mediated through 5-HT_{2A} receptor activation.

Toxicology

No studies were identified that have examined the toxicity of 25I-NBOMe *in vitro*, in animals, or in humans.

The clinical features of acute toxicity associated with 25I-NBOMe use as reported by the Member States are provided in section 3.4.1 'non-fatal intoxications' and Annex 2. These include a number of analytically confirmed cases (including those reported by Hill et al., 2013), and, in a subset, 25I-NBOMe was the only substance detected in the toxicology screen. Additional case reports/series from the United States were identified in the scientific literature (Kelly et al., 2012; Poklis et al., 2013; Rose et al., 2012; Rose et al., 2013; Stellpflug et al., 2013).

Dependence and abuse potential

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

([8]) 5-Methoxy-di-isopropyl-tryptamine
([9]) 2,5-Dimethoxy-4-iodoamphetamine
([10]) 2-(4-Chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine

Some self-reported experiences on user websites suggest re-dosing of 25I-NBOMe (e.g. Erowid, 2013a,b) although the available information does not allow for further comment.

3.4.2 Characteristics of users

No studies were identified that examined the characteristics of users of 25I-NBOMe. The section below includes a discussion of the characteristics of users which includes information from self-reported use from Internet drug discussion forums and related websites (hereafter 'user websites'). As such 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 ([11]) 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.

Route of administration, dose and drug regimens

Information provided by the Member States, as well as from case reports/series and user websites suggests the routes of administration for 25I-NBOMe include sublingual, buccal, nasal (insufflation and absorption of liquid solutions), oral, injection (intravenous and intramuscular), rectal and smoking.

Information from case reports/series and user websites suggest a range of doses are used that may depend on the route of administration. Example doses reported on the Erowid user website include: '750 ug, sublingual'; '3750 ug, sublingual'; '1000 ug, sublingual'; '1mg, buccal'; '1 blotter hit, sublingual/buccal'; '1000 ug, insufflated'; '500-1000 ug, smoked' (Erowid, 2013a). Further examples are provided in the section on 'non-fatal intoxications' (above) (see also: Drug Enforcement Administration, 2013a,b,c; Erowid, 2013a,b; Google, 2013a,b; Hill et al., 2013 ([12]); Stellpflug et al., 2013).

([11]) For example use of the street names 'legal acid' and 'Hoffman'.

([12]) In six of the seven cases reported by Hill et al. (2013), it is not clear if the patients intended to purchase and use 25I-NBOMe. The paper reports that '*Cases 2–7 had used the 25I- NBOMe together at a house party after it had been purchased via the internet. The drug had arrived by*

Information from user websites suggest that 25I-NBOMe may be used on its own as well as in combination with other new psychoactive substances and/or controlled drugs (Erowid, 2013b; Google 2013a; Google 2013b). In some of the non-fatal intoxications and deaths reported by the Member States as well as in case reports/series other new psychoactive substances and/or controlled drugs were detected in biological samples (Section 3.4.1 and Annex 2).

Subjective effects

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. Table 1 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 (2013a). Table 2 provides an overview of subjective effects of 25I-NBOMe as reported by Erowid (2013a). 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.

Table 1. Examples of self-reported duration of effects of 25I-NBOMe per route of administration (tentative) as reported by Erowid (2013a). No information on the doses that were used was provided.

Duration of effects for 25I-NBOME	**Sublingual / Buccal**	**Insufflated**
Total duration	6–10 hrs	4–6 hrs
Onset	15–120 mins	5–10 mins
Coming up	30–120 mins	10–30 mins
Plateau	120–240 mins	60–120 mins
Coming down	60–240 mins	120–180 mins
After effects	1–7 days	1–7 days
Hangover / Day After	?	?

mail as a powder enclosed in purple capsules and was labeled as '2C-B'. The '2C-B' presumably refers to 2-(4-bromo-2,5-dimethoxyphenyl)ethylamine; a ring-substituted phenethylamine which is subject to international control.

Table 2. Examples of subjective effects of 25I-NBOMe as reported by Erowid (2013a). No information on the doses that were used was provided.

Subjective effects of 25I-NBOMe	
Positive	Strong open and closed eye visuals, including trails, color shifts, brightening, etc. Mood lift Euphoria Mental and physical stimulation Increase in associative & creative thinking Increased awareness & appreciation of music Life-changing spiritual experiences Erotic, sexual thoughts and sensations Feelings of love and empathy
Neutral	General change in consciousness Pupil dilation Difficulty focusing Unusual body sensations (facial flushing, chills, goosebumps, body energy) Change in perception of time, time dilation Slight increase in heart rate Yawning, especially when coming up Does not suppress appetite
Negative	Confusion Looping Scrambled communication Nausea Insomnia Looping, recursive, out of control thinking Paranoia, fear, and panic Unwanted and overwhelming feelings Unwanted life-changing spiritual experiences Vasoconstriction, peripheral numbness, swelling of feet, hands, face

Availability, supply, price

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'.

Data from the National Drug and Alcohol Research Centre's deep web monitoring programme of the Silk Road marketplace ([13,14]) (Van Buskirk et al., 2013) identified

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

([14]) 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. See Christin (2012) for an overview of the original Silk Road.

29 retailers in early February 2013 offering compounds from the 'NBOMe family' for sale. 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 ([15]). 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 Silk Road has reopened.

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 lysergic acid diethylamide (LSD). No information was reported on the price of 25I-NBOMe when sold as LSD.

Prevalence of use

Data from prevalence surveys

No prevalence surveys were identified that have examined the use of 25I-NBOMe in the general population or in targeted populations.

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] (Global Drug Survey, 2013), although there is evidence from club outreach services that 'NBOMe' is a popular club drug and that it is mostly bought from the Internet". 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, 2013).

Information from seizures and collected samples suggests that 25I-NBOMe is being sold directly on the illicit drug market as LSD. 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 % ([16]). Last year use of LSD in this age group ranges from 0 % to 1.7 % ([17]). Last 30 days

([15]) 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. See Christin (2012) for a discussion of some of the market characteristics and dynamics of the original Silk Road.

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

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

prevalence of LSD use in this age group ranges from 0 % to 0.6 % ([18]). 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 ([19]) surveys in 2011, with only the Czech Republic reporting a prevalence level of 5 %.

3.5 Information on whether or not the new substance is currently under assessment, or has been under assessment, by the UN system — Article 5.2(e) of the Decision

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961 and the Convention on Psychotropic Substances, 1971. On 10 October 2013, the World Health Organization informed the EMCDDA that 25I-NBOMe is currently under assessment and *'the critical review report will be published only early next year (probably April)'*.

Article 7.1 of Council Decision states that '*no risk assessment shall be carried out in the absence of a Europol/EMCDDA Joint Report. Nor shall a risk assessment be carried out where the new psychoactive substance concerned is at an advanced stage of assessment within the United Nations system, namely once the WHO expert committee on drug dependence has published its critical review together with a written recommendation, except where there is significant new information that is relevant in the framework of this Decision*'.

The Joint Report has been produced on the understanding that 25I-NBOMe is not at an advanced stage of assessment within the United Nations system.

3.6 The date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol — Article 5.2(f) of the Decision

The first official EMCDDA–Europol notification of 25I-NBOMe dates from 21 June 2012 from 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 the analytical technique of GC-MS ([20]) (library match).

25I-NBOMe was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through the European Union Early Warning System and a profile of the substance was created in the EMCDDA European Database on New Drugs (EDND). Since then analytical details, background information and public

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

([19]) European school Survey Project on Alcohol and other Drugs.

([20]) Gas chromatography-mass spectrometry.

health alerts have been exchanged between EMCDDA, Europol and the Member States on an ad hoc basis. The Commission and the EMA were kept duly informed.

3.7 Information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State — Article 5.2(g) of the Decision

Five Member States (Denmark, Latvia, Slovenia, Sweden, and the United Kingdom) as well as Norway reported that 25I-NBOMe is subject to control measures under drug control legislation. In Denmark it is controlled by the generic classification of phenethylamines in the Executive Order on Euphoriant Substances. In Latvia it is controlled according to Cabinet Regulation 847 “Regulations regarding narcotic substances, psychotropic substances and precursors to be controlled in Latvia”. In Slovenia it was included in a Decree amending the Decree on classification of illicit drugs, Official Gazette of RS No. 62/2013. In Sweden it is controlled under the Narcotic drugs control Act (SFS 1992-860) and the Narcotic drugs control Ordinance (SFS 1994:1554). In the United Kingdom it was placed under a temporary class drug order in June 2013. In Norway it is controlled by the generic scheduling of phenethylamines introduced on 14 February 2013.

Four Member States (Austria, Hungary, Poland and Romania) reported that 25I-NBOMe is subject to control measures under legislation covering unauthorised supply of defined or qualifying new psychoactive substances. In Austria it is controlled under the New Psychoactive Substances Act. In Hungary it falls within the generic definition of phenethylamines in Schedule C of Government Decree 66/2012. In Poland, 25I-NBOMe falls under the definition of a ‘substitution drug’ under the Act amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection, 2010 and as such its marketing and production is penalized with a fine (administrative sanctions). In Romania it is controlled under Law 194 2011 which stipulates that all substances with psychoactive potential are subject to control until proven harmless by a special designated commission.

Two Member States (Finland and the Netherlands) reported that 25I-NBOMe is subject to control measures under medicines legislation. In Finland it has been controlled since 15 March 2013 under the Medicines Act (395/87). In the Netherlands, when sold in consumer amounts it is treated as being a medicinal product and must comply with medicinal product legislation and general product safety legislation.

Sixteen Member States (Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Ireland, Italy, Lithuania, Luxembourg, Malta, Portugal, and Slovakia) and Turkey have reported that 25I-NBOMe is not subject to control measures at the national level ([21]).

No information was provided regarding the control status of 25I-NBOMe in Spain.

([21]) Germany and Turkey reported that they intend to introduce control measures for 25I-NBOMe.

3.8 Further information — Article 5.2(h) of the Decision

3.8.1 The chemical precursors that are known to have been used for the manufacture of the substance

No information was reported by the Member States, Turkey or Norway about the chemical precursors or manufacturing methods used to make 25I-NBOMe. Methods for the production of 25I-NBOMe are documented in the scientific literature.

3.8.2 The mode and scope of the established or expected use of the new substance

No studies were identified that have examined the mode and scope of established or expected use of 25I-NBOMe. Given the limited information currently available, much of the relevant information reported by the Member States as well as that from case reports/series published in the scientific literature and from user websites has been included in the previous sections. It is important to note in this respect that information from the Member States (such as seizures, collected samples, non-fatal intoxications) and user websites suggest that 25I-NBOMe may be commonly sold as a 'legal' replacement for LSD or sold as LSD directly on the illicit drug market. As a result, the mode and scope of use of 25I-NBOMe may, in part, overlap and/or reflect the mode and scope of use of LSD. Additional research is required in order to examine to what extent the mode and scope of 25I-NBOMe use overlap and/or reflect those of LSD.

Settings of use

Briefly, information from the Member States as well as from case reports/series suggests that 25I-NBOMe may be used in a range of settings, including the home environment (where an individual is on their own or in the company of others) and recreational settings. In the latter case this includes informal settings (such as 'house parties') as well organised events (such as 'techno' music events).

The recent report on the 'NBOMe' compounds by the Advisory Council on the Misuse of Drugs in the United Kingdom noted that 'evidence from club outreach services that 'NBOMe' is a popular club drug and that it is mostly bought from the Internet' (Advisory Council on the Misuse of Drugs, 2013).

3.8.3 Other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks

No information was provided by the Member States, Turkey or Norway that indicated that 25I-NBOMe had any other use apart from legitimate scientific research and as an analytical reference standard.

Researchers have used radiolabelled ([22]) 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 imaging studies (Ettrup et al., 2010; Ettrup et al., 2011). Information on the management of health and 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.

From the available information it does not appear that 25I-NBOMe is used in the manufacture of a medicinal product in the European Union. However, the collection of information cannot be considered exhaustive in the absence of an European Union database on the synthetic routes of all medicinal products ([23]).

4. Information from the EMA as requested by Article 5.3 of the Decision

4.1 Marketing authorisation

Twenty-four Member States, Iceland and Norway responded to the EMA's information request (see section 2). They reported that the new psychoactive substance 25I-NBOMe has not obtained a marketing authorisation ([24]).The EMA also reported that the new psychoactive substance 25I-NBOMe has not obtained a marketing authorisation through the central authorisation procedure.

4.2 Application for a marketing authorisation

Twenty-four Member States, Iceland and Norway responded to the EMA's information request (see section 2). They reported that the new psychoactive substance 25I-NBOMe is not the subject of an application for a marketing authorisation ([24]). The EMA also reported that the new psychoactive substance 25I-

([22]) 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.

([23]) i.e. products that have been granted a marketing authorisation, or where an application for a marketing authorisation has been made, or where the marketing authorisation has been suspended.

([24]) Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Iceland, Ireland, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom provided responses in relation to both human and veterinary medicinal products. Cyprus, Italy, Lithuania, Malta and Slovakia provided responses in relation to human medicinal products. France, Latvia and Poland provided responses in relation to veterinary medicinal products. In addition the EMA provided information in relation to both human and veterinary medicinal products in respect to the central authorisation procedure.

NBOMe is not the subject of an application for a marketing authorisation through the central authorisation procedure.

4.3 Suspended marketing authorisation

Twenty-four Member States, Iceland and Norway responded to the EMA's information request (see section 2). They reported that there had been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance 25I-NBOMe ([24]). The EMA also reported that the new psychoactive substance 25I-NBOMe is not the subject of a suspended marketing authorisation through the central authorisation procedure.

5. Conclusion

25I-NBOMe is a substituted phenethylamine. It is a potent full agonist of the serotonin 5-HT_{2A} receptor and appears to have hallucinogenic effects. It has been available on the European Union drug market since at least May 2012 and has been detected in 23 Member States and Norway. Severe toxicity associated with its use has been reported in four Member States and one death associated with 25I-NBOMe has been analytically confirmed. Seven countries have reported that it has been sold as LSD or as a 'legal' alternative to LSD. On this basis the potential impact from the further spread of 25I-NBOMe (and related 'NBOMe' compounds) on public health is a key concern. We conclude that the health and social risks caused by the manufacture, trafficking and use of 25I-NBOMe, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure in accordance with Article 6 of Council Decision 2005/387/JHA.

References

1. Advisory Council on the Misuse of Drugs, (2013), ‘‘NBOMe’ compounds: A review of the evidence of use and harm’, Home Office. https://www.gov.uk/government/publications/nbome-compounds-a-review-of-the-evidence-of-use-and-harm

2. Aghaajanian, G.K. and Marek, G.J. (1999), ‘Serotonin and hallucinogens’, Neuropyschopharmacology, 21 pp. 16S–23S.

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

4. Braden, M.R., Parrish, J.C., Naylor, J.C., 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 pp. 1956–1964.

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

6. Drug Enforcement Administration (2013a), ‘Schedules of controlled substances: temporary placement of three synthetic phenethylamines into Schedule I’, Federal Register, 78 pp. 61991–3.

7. Drug Enforcement Administration (2013b), ‘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; 2C-C-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. Drug Enforcement Administration. http://www.regulations.gov/contentStreamer?objectId=090000648147faf9&disposition=attachment&contentType=pdf

8. Drug Enforcement Administration (2013c), ‘Schedules of controlled substances: temporary placement of three synthetic phenethylamines into Schedule I. Final order’, Federal Register, 78 pp. 68716–9.

9. Egan, C.T., Herrick-Davis, K., Miller, K., Glennon, R.A., Teitler, M. (1998), ‘Agonist activity of LSD and lisuride at cloned 5HT$_{2A}$ and 5HT$_{2C}$ receptors’, Psychopharmacology, 136 pp. 409–414.

10. 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

11. Erowid (2013a), http://www.erowid.org/chemicals/2ci_nbome/2ci_nbome_effects.shtml

12. Erowid (2013b), http://www.erowid.org/experiences/subs/exp_2CINBOMe.shtml

13. Ettrup, A., Hansen, M., Santini, MA., Paine, J., Gillings, N., Palner, M., Lehel, S., Herth, M.M., Madsen, J., Kristensen, J., Begtrup, M., 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 pp. 681–693.

14. Ettrup, A., Palner, M., Gillings, N., Santini, M.A., Hansen, M., Kornum, B.R., Rasmussen, L.K., Någren, K., Madsen, J., Begtrup, M., 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 pp. 1763–1770.

15. González-Maeso, J., Weisstaub, N.V., Zhou, M., Chan, P., Ivic, L., Ang, R., Lira, A., Bradley-Moore, M., Ge, Y., Zhou, Q., Sealfon, S.C., Gingrich, J.A. (2007), 'Hallucinogens recruit specific cortical 5-HT($_{2A}$) receptor-mediated signaling pathways to affect behavior', Neuron, 53 pp. 439–452.

16. Google (2013a), https://www.google.com/search?q=site:bluelight.ru+25I-NBOMe&ie=UTF-8&oe=UTF-8

17. Google (2013b), https://www.google.com/search?q=site:drugs-forum.com+25I-NBOMe&ie=UTF-8&oe=UTF-8

18. Halberstadt, A.L., Geyer, M.A. (2013), 'Effects of the hallucinogen 2,5-dimethoxy-4-iodophenethylamine (2C-I) and superpotent N-benzyl derivatives on the head twitch response', Neuropharmacology, 77C pp. 200–207.

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

20. Hill, S.L., Doris, T., Gurung, S., Katebe, S., Lomas, A., Dunn, M., Blain, P., Thomas, S.H. (2013), 'Severe clinical toxicity associated with analytically confirmed recreational use of 25I-NBOMe: case series', Clinical Toxicology, 51 pp. 487–92.

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

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

23. Nichols, D.E., Frescas, S.P., Chemel, B.R., Rehder, K.S., Zhong, D., 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 pp. 6116–6123.

24. Poklis, J.L., Devers, K.G., Arbefeville, E.F., Pearson, J.M., Houston, E., Poklis, A. (2013) 'Postmortem detection of 25I-NBOMe [2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine] in fluids and tissues determined by high performance liquid chromatography with tandem mass spectrometry from a

traumatic death', Forensic Science International. doi:10.1016/j.forsciint.2013.10.015

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

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

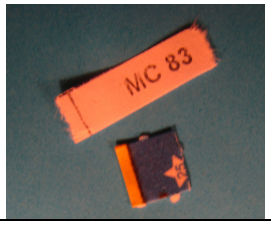
27. Stellpflug, S.J., Kealey, S.E., Hegarty, C.B., Janis, G.C. (2013), '2-(4-Iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe): Clinical case with unique confirmatory testing', Journal of Medical Toxicology. doi:10.1007/s13181-013-0314-y

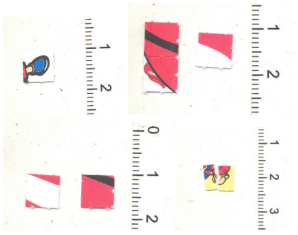
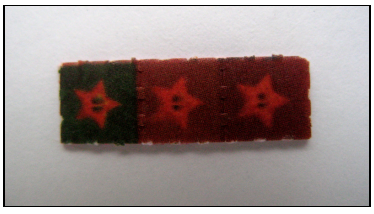
28. Van Buskirk, J., Roxburgh, A., Bruno, R., Burns, L. (2013). Drugs and the Internet, Issue 1, August 2013. Sydney: National Drug and Alcohol Research Centre. http://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/DrugsTheInternet_Newsletter%20FINAL%20with%20ISSN.pdf

Annex 1

EMCDDA–Europol Joint Report on a new psychoactive substance: 25I-NBOMe

Images of 25I-NBOMe from seizures and collected samples

Country	Image	Description
Austria		**Collected sample, analysed in February 2013** one blotter, sold as LSD (street name "DOC") Contents: 25I-NBOMe and an unknown substance Collecting authority: ChEckiT!
Austria		**Collected sample, analysed in February 2013** one blotter, sold as LSD (street name "Hoffmann") Collecting authority: ChEckiT!
Austria		**Collected sample, analysed in March 2013** three blotters, sold as LSD (4-10€). Contents: amphetamine (95 mg/g), caffeine (65 mg/g), Collecting authority: ChEckiT!
Italy		**Seizure, January 2013** 8 blotters, seized in Bologna. Seizing authority: State Police of Bologna.
Latvia		**Seizure, October 2013** 124 impregnated paper fragments, seized in Daugavpils. Seizing authority: Forensic service department by State police

Country	Image	Description
Norway		**Seizure, March 2012** 250 squares of paper, seized in Stavanger. Seizing authority: Norwegian police
Norway		**Seizure, February 2013** 1 piece of blotter paper, consisting of 59 squares with size: 1 x 1cm, seized in Ålesund. Seizing authority: Norwegian Customs
Poland		**Seizures, May 2012** 5,4g of powder (package declared as containing 1-Bromoindoline), seized in Kraków. Seizing authority: Customs Services Warsaw
Poland		**Seizures, March and April 2013** stamps, seized in Łódź, Kraków and Katowice.
Romania		**Seizure, October 2013** blotter paper, seized in Alba Iulia. Seizing authority: Romanian police

Country	Image	Description
United Kingdom		**Seizure, May 2013** 19 apparent LSD tabs, seized in North East of Scotland.

Annex 2 — Non-fatal and fatal intoxications associated with 25I-NBOMe

Country	Date of intoxication (gender, age)	Biological sample	25I-NBOMe result ([1])	Results for other substances ([2])	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

Country	Date of intoxication (gender, age)	Biological sample	25I-NBOMe result ([1])	Results for other substances ([2])	Notes
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
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

Country	Date of intoxication (gender, age)	Biological sample	25I-NBOMe result ([1])	Results for other substances ([2])	Notes
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
United Kingdom	May 2013 (M, 22)	Blood (post-mortem)	+	Amphetamine, ketamine, lignocaine, 5-MeO-DiPT, DOI, 25C-NBOMe and 2C-I	**Fatal intoxication** Cause of death: drowning

1 A '+' in this column indicates 25I-NBOMe was detected but no quantification was provided.
2 2C-I is 2,5-dimethoxy-4-iodophenethylamine
5-MeO-DiPT is 5-methoxy-di-isopropyl-tryptamine
DOI is 2,5-dimethoxy-4-iodoamphetamine
25C-NBOMe is 2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine