European Monitoring Centre
for Drugs and Drug Addiction

Risk Assessment Report
of a new psychoactive substance:

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

(25I-NBOMe)

In accordance with Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances

1. Introduction

This *Risk Assessment Report* presents the summary findings and the conclusions of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (*25I-NBOMe*). The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the *Risk assessment of new psychoactive substances: Operating guidelines* ([1]). It is written as a stand-alone document which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Committee. A list of the information resources considered by the Scientific Committee, including a detailed *Technical Report* on 25I-NBOMe, is provided below.

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ([2]) (hereafter 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' ([3])) that may pose public-health and social threats, including the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances ([4]) that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ([5]).

25I-NBOMe was first identified in a seizure made by Swedish Police in May 2012 and formally notified to the Early Warning System in June 2012 by Sweden. Following an assessment of the available information on 25I-NBOMe, and in accordance with Article 5 of the Council Decision, on 16 December 2013 the EMCDDA and Europol submitted to the Council of the European

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([1]) EMCDDA, (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/html.cfm/index100978EN.html

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

([3]) The information exchange mechanism laid down by the Council Decision is operationalized as the *European Union Early Warning System on New psychoactive Substances ('Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Retiox National Focal Points in the Member States, the European Commission and the European Medicines Agency.

([4]) According to the definition provided by the Council Decision, a 'new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; 'new narcotic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

([5]) In compliance with the provisions of the 1961 United Nations Single Convention on Narcotic Drugs and the 1971 United Nations Convention on Psychotropic Substances.

Union, the European Commission and the European Medicines Agency (EMA) a *Joint Report* on 25I-NBOMe ([6]). Taking into account the conclusion of the *Joint Report*, and in accordance with Article 6 of the Council Decision, on 29 January 2014, the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of 25I-NBOMe was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of five additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of 25I-NBOMe, including health and social risks. Furthermore, two experts from the Commission, one expert from Europol and one expert from the EMA participated in the risk assessment. The meeting took place on 1 and 2 April 2014 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMA. A list of the extended Scientific Committee, as well as the list of participants attending the risk assessment meeting is annexed to this report (Annex 1).

For the risk assessment, the extended Scientific Committee considered the following information resources:

(i) *Technical report on 2-(4-iodo-2,5-dimethoxyphenyl)*-N-*(2-methoxybenzyl)ethanamine (25I-NBOMe) (Annex 2)*;

(ii) *EMCDDA–Europol Joint report on a new psychoactive substance: 25I-NBOMe (2-(4-iodo-2,5-dimethoxyphenyl)*-N-*(2-methoxybenzyl)ethanamine)*;

(iii) Scientific articles, official reports, grey literature, Internet drug discussion forums and related websites (hereafter, 'user websites');

(iv) Data from EMCDDA Internet monitoring of suppliers (that typically appear to be manufacturers and/or wholesalers) and retailers selling 25I-NBOMe;

(v) *Risk assessment of new psychoactive substances: Operating guidelines;* and,

(vi) *Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances*.

Finally, it is important to note that this *Risk Assessment Report* contains a discussion of the available information on non-fatal intoxications and deaths associated with new psychoactive

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

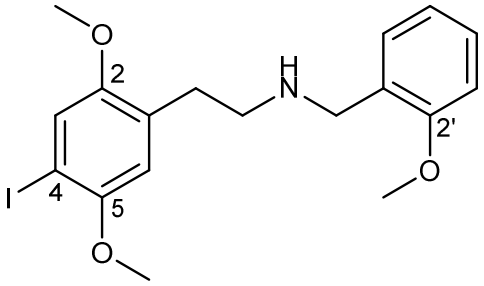
substances that are critical to the identification of emerging toxicological problems within the European Union. In this context, it is important to recognise that the capacity to detect, identify and report these events differs both within and between the Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. As a result, more information is available; however, it is likely that serious adverse events remain under-detected.

2. Physical and chemical description of 25I-NBOMe and its mechanisms of action, including its medical value

25I-NBOMe is a ring-substituted phenethylamine substance which is further substituted at the nitrogen atom with a 2-methoxybenzyl moiety; it was invented in the early 2000s (Figure 1). The systematic (International Union of Pure and Applied Chemistry, IUPAC) name of 25I-NBOMe is 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine. 25I-NBOMe is a synthetic derivative of the classical serotonergic hallucinogen 2C-I ([7]), which was subject to a risk assessment at the European Union level in 2003 ([8]).

The phenethylamine nucleus shows the classical 2,4,5-trisubstitution pattern and a number of positional isomers are possible. Such compounds have not yet been notified to the Early Warning System.

Figure 1. The molecular formula, weight, and monoisotopic mass of 25I-NBOMe.



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

Molecular weight: 427.28 g/mol (base)

Monoisotopic mass: 427.0644 Da

The free base has been described as a colourless oil and the hydrochloride salt form is a white powder soluble in water. The chemical forms of 25I-NBOMe detected ([9]) in seizures and collected samples are unknown. 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,

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([7]) 2-(4-iodo-2,5-dimethoxyphenyl)ethanamine

([8]) 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

([9]) 'Detections' is an all-encompassing term, which 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.)

single-dose units. There are also reports of seizures in powder and in liquid form. It has been suggested that 25I-NBOMe may be complexed with cyclodextrin to improve buccal absorbtion; however, to date there has been no analytical confirmation of such a form reported to the Early Warning System.

The tentative 'common doses' of 25I-NBOMe reported by users are: 500 - 800 µg (both sublingual/buccal and insufflation). For sublingual/buccal administration, the tentative onset of desired effects is typically reported within 15–120 minutes with desired effects lasting up to 6–10 hours, and for insufflation the onset is reported within 5–10 minutes with desired effects lasting up to 4–6 hours.

In most cases, 25I-NBOMe was reported as the only active substance present in the samples analysed; in about 10% of detections it was found in combination with other substances, including other 'NBOMe' analogues (25B-NBOMe, 25C-NBOMe, 25H-NBOMe and 25N-NBOMe), 2C-B, 2C-C, 2C-I, 2C-T-4, mescaline and lysergic acid diethylamide (LSD). No quantitative analyses were available.

The detection of 25I-NBOMe by gas chromatography (GC) and liquid chromatography (LC) coupled with mass spectrometry (MS) is straightforward with suitable equipment and analytical reference material. Due to its high potency and therefore expected use of small amount of the drug by users, the analyses of biological samples require highly sensitive techniques (e.g. tandem mass-spectrometry). Currently, 25I-NBOMe is associated with the *ortho*-substituted *N*-(2-methoxybenzyl) group but both the *meta*- and *para*-substituted analogues, i.e. *N*-(3-methoxybenzyl) and *N*-(4-methoxybenzyl) are possible. The implementation of chromatographic techniques may be suitable to obtain unambiguous differentiation. No information was provided regarding the possible presence of the other isomers on the drug market.

There have been several *in vitro* and animal studies which have investigated the pharmacodynamics of 25I-NBOMe. Vascular and cell-based assays have shown that 25I-NBOMe displays low nanomolar (nM) affinity towards the 5-HT_{2A} receptor. In addition studies on functional activity also suggest that 25I-NBOMe is a full agonist at this receptor. The addition of the *N*-(2-methoxybenzyl) group has been shown to increase binding affinity and potency at this subtype receptor when compared to 2C-I.

As noted above, 25I-NBOMe has been shown to be 5-HT_{2A} receptor agonist using a number of vascular assays (e.g. rat tail artery) which was measured by the extent of vasoconstriction. Here, 25I-NBOMe was shown to be a partial agonist (activity around 30% of 5-HT). Further studies are required in order to determine what relevance this may have in humans.

Reports from user websites as well as clinical observations of individuals who have used 25I-NBOMe suggest that is has hallucinogenic effects. Consistent with these observations are data from animal studies that have examined the effect of 25I-NBOMe on the head twitch behavioural response (HTR) in mice. This response is used as a surrogate marker of the hallucinogenic effect of 5-HT_{2A} receptor activation in humans. 25I-NBOMe produced a robust and potent HTR in mice which was antagonised by the potent 5-HT_{2A} receptor antagonist volinanserin. 25I-NBOMe was ten-fold more potent in this model compared to 2C-I and slightly less potent than LSD. Appreciable affinities have also been observed for 5-$HT_{1A/2B/2C}$, 5-HT_6, dopamine D_3, D_4, α_{2C} adrenoceptor and serotonin transporter (SERT).

Detailed pharmacokinetic data for 25I-NBOMe in animals and humans are currently not available. Data obtained from the analysis of biological samples indicate that O-demethylation (position to be confirmed) may be an important feature. The O-demethylated *N*-(2-hydroxybenzyl) analogue has been shown to be a potent 5-HT receptor agonist although further research is required to confirm the extent to which this substance may form during metabolism. 25H-NBOMe, i.e. the de-iodinated analogue, may also be formed during metabolism but further studies are needed to exclude its detection as a potential contaminant present in the consumed drug. A recently published *in vitro* study carried out in human microsomal preparations found that 25I-NBOMe showed significant intrinsic clearance normally associated with extensive first pass metabolism and insufficient bioavailability. However, further studies are needed to investigate whether 25I-NBOMe is orally active or not due to observations from clinical case reports ([10]) and self-reported experiences on user websites which suggest that oral ingestion is used as a route of administration. Limited information is available from self-reports that may provide an indication of the pharmacokinetic parameters such as time of onset of desired effects, adverse effects, or duration of action of 25I-NBOMe.

No animal studies were identified that investigated the median lethal dose (LD_{50}) of 25I-NBOMe.

No animal studies were identified that investigated the potential for self-administration of 25I-NBOMe.

No human studies were identified that investigated the psychological and/or behavioural effects of 25I-NBOMe. Information on these effects from clinical case reports as well as medical examiner and/or post-mortem toxicology reports are discussed below.

25I-NBOMe is used in scientific research to study the serotonergic system. [^{11}C] 25I-NBOMe is being studied as a potential radiolabelled tracer for Positron Emission Tomography (PET) imaging. 25I-NBOMe is also used in research investigating its chemistry, pharmacology and toxicology as a result of its emergence on the drug market. In addition, 25I-NBOMe is used in analytical reference materials. There are currently no known uses of 25I-NBOMe as an industrial, agricultural or cosmetic compound. There is no marketing authorisation (existing, on-going or suspended) for 25I-NBOMe in the European Union nor in the Member States that responded to the information request by the EMA that was launched under Article 5 of the Council Decision. There is no information to suggest that 25I-NBOMe is used in the manufacture of a medicinal product in the European Union. However, it should be noted that there is no European Union database on the synthetic routes of all registered medicinal products.

3. Chemical precursors that are used for the manufacture of 25I-NBOMe

The synthesis of 25I-NBOMe was first published in 2003 and was based on a classical reductive alkylation procedure where the primary amine starting material, i.e. 2C-I in this particular case, was reacted with 2-methoxybenzaldehyde to give an imine intermediate, which could be by itself used as a precursor. Once this was formed, a reducing agent (in this case $NaBH_4$) was employed to yield 25I-NBOMe. Modification of the primary amino group may also include the

([10]) The term 'clinical case reports' is used to denote both clinical case reports and case series published in the scientific literature.

reaction with a corresponding benzyl, benzoyl halide or benzoic acid. Other methods of synthesis may be used.

There is currently no information regarding manufacturing sites, the chemical precursors or the synthetic routes used for 25I-NBOMe that has been detected on the drug market. A seized sample was found to contain an *N,N*-dibenzylated NBOMe. There is no additional information on impurities and side-products from seizures and collected samples.

4. Health risks associated with 25I-NBOMe

Individual health risks

The assessment of individual health risks includes a consideration of the acute and chronic toxicity of 25I-NBOMe, as well as its dependence producing potential, and its similarities to and differences from other chemically or pharmacologically related substances.

It is important to note that when interpreting the information from non-fatal intoxications and deaths reported by the Member States as well as from clinical case reports and user websites, individuals may have used other pharmacologically active substances in addition to 25I-NBOMe. The presence of other substances may account for some the reported effects.

Despite the structural similarities of 25I-NBOMe to 2C-I and other 2,4,5-trisubstituted phenethylamines and phenylisopropylamines, and the high affinity binding of 25I-NBOMe to the 5-HT_{2A} receptor it is difficult to predict the pharmacological and toxicological profile of 25I-NBOMe based on a comparison with these substances due to potential differences in mode and mechanisms of action.

Based on the limited information from clinical case reports and user websites, the routes of administration for 25I-NBOMe may include sublingual, buccal (especially “blotter” paper), nasal (insufflation and absorption of liquid solutions), oral, injection (intravenous and intramuscular), rectal and smoking. The available information suggests that a range of doses are used which in part depends on the route of administration. It is important to note in this respect that doses of 25I-NBOMe found on blotters may range between high µg to low mg levels.

There is some suggestion that 25I-NBOMe has been sold as a replacement for the internationally controlled hallucinogenic substance LSD which is also commonly taken sublingually in the form of blotters. The fact that 25I-NBOMe shows psychoactive properties in humans at low dosage levels (e.g. < 1 mg) appears to reflect its potency *in vivo*. It also appears to be sold as a ‘research chemical’ or equivalent products by Internet retailers as well as products that are clearly stated to be 25I-NBOMe ‘tabs’.

25I-NBOMe may be used on its own or in combination with other substances, including other psychoactive substances. Analysis of various seized and collected products has shown that the composition of the products can differ and the user is unlikely to be aware of the exact dose or compound(s) present.

Detections reported by the Member States to the Early Warning System have highlighted that 25I-NBOMe may also be encountered in liquid or powdered form. These physical forms may affect the potential for acute toxicity as well as the clinical profile thereof. For example, due to its

high potency, nasal insufflation of powdered 25I-NBOMe may increase the risk of (serious) adverse events.

In addition to the manifestation of psychoactive effects commonly observed with serotonergic hallucinogens (e.g. LSD, psilocybin or 2C-B (2,5-dimethoxy-4-bromophenethylamine)), clinical case reports also indicate the potential for inducing severe agitation, confusion and a significant stimulant effect which may also be associated with serotonergic toxicity (serotonin syndrome).

Information from clinical case reports suggest that some users experience severe psychological and behavioural changes associated with 25I-NBOMe use. These include intensive auditory and visual hallucinations, severe agitation, aggression and unpredictable violent episodes which in some cases may have played a role in accidents and self-induced trauma. This includes three cases from the United States where medical examiner and/or post-mortem toxicology reports suggested that 25I-NBOMe toxicity led to unpredictable, violent behaviour resulting in death.

It is difficult to predict with accuracy any particular potential interactions with other drugs and medicinal products. However, given that 25I-NBOMe is a full agonist at the 5-HT_{2A} receptor and has agonist activity at other 5-HT receptors, there is a concern for potential interactions with other substances that act on the serotonergic system. This includes the use of medicinal products (e.g. selective serotonin reuptake inhibitors (SSRIs)) and/or substances known to increase serotonin release and/or block reuptake which may increase the risk of developing serotonergic toxicity, the symptoms of which can include tachycardia, hypertension, hyperthermia, muscle rigidity and convulsions.

There have been 32 non-fatal intoxications associated with 25I-NBOMe that were reported by four Member States to the Early Warning System: Belgium (3 cases), Poland (4), Sweden (18), and the United Kingdom (7). 15 of these have been analytically confirmed.

There have been 4 deaths associated with 25I-NBOMe that were reported by three Member States: Belgium (2 deaths), Poland (1) and the United Kingdom (1). Two of these have been analytically confirmed; in one of these cases the cause of death was reported as ‘natural causes’, in the other it was reported as ‘drowning’. Additional information is not available to comment further. There is a report from the United States about an 18-year old person who died after ingesting 25I-NBOMe sold as LSD. The cause of death was given as acute 25I-NBOMe poisoning; no alcohol, prescription drugs or other illicit drugs were found in post-mortem samples.

There are no published animal or human studies that have investigated the potential for neurotoxicity, reproductive toxicity, genotoxicity and carcinogenic potential of 25I-NBOMe. No studies have examined the chronic toxicity of 25I-NBOMe in animals or humans.

There are no published studies on the abuse liability or dependence potential of 25I-NBOMe.

There is no information on the psychosocial consequences of chronic 25I-NBOMe use such as effects on psychological development and the interaction with the social environment.

Public health risks

The public health risks associated with 25I-NBOMe may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences.

In some cases, 25I-NBOMe is sold and consumed as a substance in its own right. Similar to other hallucinogenic drugs, users may combine 25I-NBOMe with other psychoactive substances (e.g. entactogens, stimulants and/or depressants including alcohol and medicines) both intentionally and unintentionally. As noted, there is no information on the purity of 25I-NBOMe that is present on the drug market. In some of the seizures 25I-NBOMe has been reported to be the only psychoactive substance detected; in about 10% of detections it was found in combination with other substances. No quantitative analyses were available. It is important to note that analysis of various new psychoactive substances sold on the market have shown that the composition, including dose, can differ both over time and geographical location and, as a result, it is unlikely that the user will be aware of the exact dose or compound being ingested (by whatever route) which presents an inherent risk to the individual.

25I-NBOMe is openly marketed and sold on the Internet as a ‘research chemical’. EMCDDA monitoring of Internet suppliers and retailers selling 25I-NBOMe (conducted in the month prior to the risk assessment) identified more than fifteen companies that may be based within the European Union and China, offering up to kilogram quantities of the substance. In some non-fatal intoxications reported by the Member States as well as clinical case reports it was reported that the users had sourced 25I-NBOMe from the Internet.

Information from seizures, collected samples, user websites and Internet retailers suggest that 25I-NBOMe is sold as a drug in its own right and marketed as a "legal" replacement for LSD. In addition it is also sold as LSD on the illicit drug market. In this latter case users may be unaware that they are using 25I-NBOMe.

The main route of 25I-NBOMe administration appears to be buccal or sublingual. Injection of 25I-NBOMe appears to be less common; sharing of injecting equipment carries the risk of bacterial infections and the transmission blood-borne viruses. Due to the high potency of 25I-NBOMe, use of powders and liquids are likely to make it difficult for users to, may increase the risk of serious adverse events.

Information from the Member States as well as from clinical case reports suggests that 25I-NBOMe may be used in a range of settings. These include the home environment as well as recreational settings, such as informal settings (such as ‘house parties’) and organised events (such as music festivals).

There are currently no co-ordinated national or European population surveys on 25I-NBOMe use.

One non-representative Internet survey open to respondents across the World described the characteristics of users of 25B-NBOMe, 25C-NBOMe and 25I-NBOMe. A total of 22 289 responses were collected in late 2012. 33.9% of respondents were from the UK, 35.9% were from Australia, 17.3% were from the USA, 10.0% were from the rest of Europe, and 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% (n = 582) of respondents reported having ever tried one of the three NBOMe drugs and that at 2.0% (n = 442), 25I-NBOMe was the most popular followed by 25B-NBOMe at 1.2% and 25C-NBOMe at 0.8%. Almost all respondents (93.5%) whose last new drug tried was an NBOMe drug tried it in 2012 and 81.2% of this group administered the drug orally or sublingually/buccally. More than half (56.7%) of NBOMe users in the preceding 12 months were from the USA, 21.3% were from the UK, 10.2% were from the 'Euro-Zone', 9.8% were from Australia and 2.1% 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 drug source (41.7%) was the Internet.

According to information provided by club outreach services in the recent review of the NBOMe compounds (including 25I-NBOMe) by the United Kingdom Advisory Council on the Misuse of Drugs (ACMD), 'NBOMe are popular club drugs and that are it is mostly bought from the Internet' [sic]. Conversely, another source of information cited therein noted that the 'prevalence of NBOMe compounds is very low in surveys with young adults conducted in nightclubs and festivals'.

As noted, information from seizures and collected samples suggests that 25I-NBOMe is being sold on the illicit drug market as LSD. This coupled with its availability in kilogram quantities from Internet suppliers and retailers raises the possibility that users could use 25I-NBOMe as a (temporary) replacement for LSD. While the extent of this practice is unclear it may be relevant to consider the prevalence of LSD use in Europe. Among young adults (15- to 34-year-olds), lifetime prevalence of LSD use 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 in European school Survey Project on Alcohol and other Drugs (ESPAD) surveys in 2011, with only the Czech Republic reporting a prevalence level of 5 %.

5. Social risks associated with 25I-NBOMe

There is limited information on the social risks associated with 25I-NBOMe.

There is no information on whether the use of 25I-NBOMe affects education or career, family or other personal or social relationships or leads to marginalisation.

([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

Although there are no relevant studies, it may be assumed that the acute behavioural effects of 25I-NBOMe on operating machinery and driving are similar to those caused by other potent hallucinogenic substances.

Limited information from clinical case reports suggest that some users experience severe psychological and behavioural changes associated with 25I-NBOMe use. While these appear to have been limited to accidents and self-induced trauma, it is not possible to exclude that violent behaviour could be directed at others.

There is no information on the social risk associated with the distribution and trafficking of 25I-NBOMe.

It is not possible at this time to estimate whether 25I-NBOMe is associated with greater health care costs than other hallucinogenic drugs.

6. Information on the level of involvement of organised crime and information on seizures and/or detections by the authorities, and the manufacture of 25I-NBOMe

There is no information to suggest the involvement of organised crime or criminal groups in the manufacture, distribution (trafficking) and supply of 25I-NBOMe. EMCDDA targeted Internet monitoring of suppliers and retailers selling 25I-NBOMe has identified a number of companies that may be based within the European Union and China, offering kilogram quantities of the substance.

7. Information on any assessment of 25I-NBOMe in the United Nations system

The World Health Organization is the specialised agency of the United Nations designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the 1961 United Nations Single Convention on Narcotic Drugs, and the 1971 United Nations Convention on Psychotropic Substances.

The World Health Organization informed the EMCDDA that 25I-NBOMe will be subject to evaluation at the thirty-sixth meeting of the Expert Committee on Drug Dependence, which will be held in June 2014.

Article 7.1 of Council Decision states:

'*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 risk assessment has been carried out on the understanding that 25I-NBOMe is not at an advanced stage of assessment within the United Nations system.

8. Description of the control measures that are applicable to 25I-NBOMe in the Member States

25I-NBOMe is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs or in the 1971 United Nations Convention on Psychotropic Substances (together 'UN drug conventions').

Six Member States (Denmark, Latvia, Lithuania, Slovenia, Sweden, and the United Kingdom) as well as Norway control 25I-NBOMe under legislation by virtue of their obligations under the UN drug conventions.

Twenty-two Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, and Spain) and Turkey do not control 25I-NBOMe by virtue of their obligations under the UN drug conventions ([14]).

Of these 22 Member States, 7 (Austria, Finland, Hungary, Netherlands, Poland, Romania and Spain) use other legislative measures to control 25I-NBOMe. In Austria it is controlled under the New Psychoactive Substances Act. Finland uses medicines legislation to control 25I-NBOMe. In Hungary it falls within the generic definition of phenethylamines in Schedule C of Government Decree 66/2012. In the Netherlands medicines legislation is used to control 25I-NBOMe. 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 it's 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. Spain reported that although there is no current specific legislation controlling production, commerce, imports, exports or use/consumption of 25I-NBOMe, given that it may cause harmful effects to users there is general (administrative and criminal) legislation on health protection which, if necessary, is fully applicable.

9. Options for control and the possible consequences of the control measures

Under Article 9.1 of the Council Decision, the option for control that is available is for the Member States to submit the new psychoactive substance 25I-NBOMe to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the UN drug conventions. There are no studies on the possible consequences of such control measures on 25I-NBOMe. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of 25I-NBOMe and hence the further expansion of the current open trade in this substance. However, this may have little impact on the manufacturers and suppliers based outside of the European Union.

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

- A health consequence that may result from this control option is the benefit brought about by the presumed reduction in availability and use.

- This control option could facilitate the detection, seizure and monitoring of 25I-NBOMe related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies within the European Union.

- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement and the courts.

- This control option could lead to replacement with other (established or new) psychoactive substances which may in themselves have public health consequences.

- It is not possible to gauge to what extent this control is likely to impact on current and future research by research/academic institutes, pharmaceutical or chemical industries. It should be noted that 25I-NBOMe is used as a tool to study the serotonergic system as part of work that aims to further the understanding of the pathogenesis of human disease. This includes research into the potential use of [^{11}C] 25I-NBOMe as a tracer in Positron Emission Tomography imaging studies.

- This control option could create an illicit market in 25I-NBOMe with the increased risk of associated criminal activity, including organised crime.

- It is a concern that Internet retailers within the European Union offer price discounts and other promotions in order to dispose of remaining stocks of new psychoactive substances when control measures are impending. Therefore, this control option could lower the price of any 25I-NBOMe that is still available on the market and temporarily increase its availability. The extent to which this will impact on public health, criminality or levels of use is difficult to predict.

In order to examine the consequences of control, the Committee wishes to note that should this option be pursued it will be important to monitor for the presence of 25I-NBOMe on the market post-control.

Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include medicines legislation or restricting the importation and supply of the substance.

10. Conclusion

25I-NBOMe is a ring-substituted phenethylamine substance which is further substituted at the nitrogen atom with a 2-methoxybenzyl moiety. It is a potent synthetic derivative of 2C-I with hallucinogenic properties. 2C-I was subjected to control measures in the Member States following a risk assessment in 2003. 25I-NBOMe was first identified in a seizure made by Swedish Police in May 2012 and formally notified to the Early Warning System in June 2012 by Sweden. 25I-NBOMe has emerged on the ‘legal highs’ market where it is sold as a ‘research

chemical' by Internet retailers; it is also sold as LSD. While 25I-NBOMe has mostly been detected in blotters, bulk quantities of powder have also been encountered.

25I-NBOMe has been detected in 23 Member States and Norway. EMCDDA monitoring of Internet suppliers and retailers selling 25I-NBOMe identified more than fifteen companies that may be based within the European Union and China, offering up to kilogram quantities of the substance.

Data on prevalence are limited to one non-representative Internet survey. Limited information suggests that 25I-NBOMe is used by groups interested in using hallucinogenic substances, including groups that have used LSD. However, further information on the size of the demand and the characteristics of these groups is not available. There is no specific information on the social risks that may be related to 25I-NBOMe.

25I-NBOMe is commonly consumed via sublingual or buccal administration of blotters. However, due to its high potency, the use of powders and liquids, in which it will be more difficult to limit the dose taken, may increase the risk of serious adverse events. The acute toxicity of 25I-NBOMe appears to include symptoms also observed with other serotonergic hallucinogens. These include auditory and visual hallucinations, severe agitation and confusion; a significant stimulant effect has also been reported which may also be associated with serotonergic toxicity. In addition, given the currently known pharmacological profile, there is a possibility of interactions with other substances which act on the serotonin system; these require further research.

25I-NBOMe either alone or in combination with one or more substances has been associated with 32 non-fatal intoxications in four Member States and in 4 deaths in three Member States. Limited information from clinical case reports suggest that some users experience severe psychological and behavioural changes associated with 25I-NBOMe use. While these appear to have been limited to accidents and self-induced trauma, it is not possible to exclude that violent behaviour could be directed at others.

There is no information to suggest the involvement of organised crime in the manufacture, distribution (trafficking) and supply. It is known to be sold on the illicit drug market as LSD. There is no information to suggest that 25I-NBOMe is manufactured in the European Union. The chemical precursors and the synthetic routes used to manufacture the 25I-NBOMe detected in the European Union are unknown although a commonly used method of synthesis includes the use of 2,5-dimethoxy-4-iodophenethylamine (2C-I) as the starting material. Although not currently under international control, 2C-I is controlled at the European Union level.

25I-NBOMe has no established or acknowledged medical use (human or veterinary) in the European Union. It is used in scientific research, particularly in the field of neurochemistry and in analytical reference materials. There is a potential that radiolabelled [^{11}C] 25I-NBOMe could be developed for use in scientific and medical imaging in humans.

25I-NBOMe is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs nor in the 1971 United Nations Convention on Psychotropic Substances. It is currently under assessment by the United Nations system. Six Member States and Norway control 25I-NBOMe under drug control legislation. Seven Member States control 25I-NBOMe under other legislation.

Many of the questions posed by the lack of evidence on the health and social risks of 25I-NBOMe, as for any new psychoactive substance, could be answered through further research. Areas where additional information would be important include: receptor binding and functional activity studies; metabolic pathway studies; behavioural studies; clinical patterns of acute and chronic toxicity in humans; the potential interaction between 25I-NBOMe and other substances (in particular those that affect the serotonergic system); prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); market studies; chemical profiling studies; the abuse liability and dependence potential; and, the social risks associated with its use.

The Committee notes that a decision to control this drug has potential positive consequences in terms of reducing availability and therefore the adverse health and social consequences arising from the use of 25I-NBOMe. It is important, however, to anticipate and minimise where possible any potential negative consequences of control. Control measures could extend an illegal market in 25I-NBOMe with the associated risk of criminal activity and may lead to the manufacture and use of other chemically related substances, of which there are many. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Finally, control should not inhibit the gathering and dissemination of accurate information on 25I-NBOMe to users and to relevant professionals.

11. List of annexes

Annex 1: List of participants attending the risk assessment meeting.

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

European Monitoring Centre
for Drugs and Drug Addiction

Annex 1. List of participants at the Risk Assessment meeting on 25I-NBOMe, 1 and 2 April 2014

A. Extended Scientific Committee

Scientific Committee Members

Dr. Anne-Line BRETTEVILLE JENSEN
Norwegian Institute for Alcohol and Drug Research, Oslo

Prof. Dr. Gerhard BUEHRINGER
Addiction Research Unit, Dep. of Clinical Psychology and Psychotherapy, Technische Universität Dresden
Institut für Therapieforschung (IFT), Munich
Vice-Chair of the Scientific Committee

Dr. Catherine COMISKEY
Director, Centre for Practice and Healthcare Innovation, Trinity College Dublin, School of Nursing and Midwifery, Dublin

Dr. Paul DARGAN
Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

Prof. Gabriele FISCHER
Medical University Vienna, Center of Public Health, Department of Psychiatry & Psychotherapy, Vienna

Prof. Dr. Henk GARRETSEN
Faculty of Social and Behavioural Sciences, Tilburg University, LE Tilburg

Prof. Dr. Matthew HICKMAN
Social Medicine, Bristol

Prof. Dr. Krzysztof KRAJEWSKI
Department of Criminology, Jagiellonian University, Krakow

Prof. Letizia PAOLI
LINC, Leuven Institute of Criminology, University of Leuven Faculty of Law, Leuven

Dr. Fernando RODRIGUEZ de FONSECA
Fundación IMABIS, Hospital Carlos Haya, Málaga

Prof. Dr. Brice De RUYVER
Department of Criminal Law and Criminology, Faculty of Law, Universiteit Gent

Prof. Dr. Rainer SPANAGEL
Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Additional Experts to the Scientific Committee

Dr. Peter BLANCKAERT
Belgian Early Warning System on Drugs, DO Public Health&Surveillance, Substance use & related disorders (SURD), Brussels

Dr. Simon BRANDT
School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Prof. Desmond CORRIGAN
The School of Pharmacy & Pharmaceutical Sciences, Trinity College, Dublin

Prof. Gaetano DI CHIARA
Cagliari University, Biomedical Sciences Department, Cagliari

Dr. Daríusz ZUBA
Institute of Forensic Research, Krakow

Institutional Representatives

European Commission
Elsa MAIA
Anti-Drugs Policy Unit, European Commission, Brussels

Fabiano RENIERO
Joint Research Centre, Institute for Health and Consumer Protection (IHCP), Brussels

European Medicines Agency (EMA)
Jean-Marc VIDAL
Scientific Support and Projects, Non-clinical Safety, Human Medicines Evaluation Division, London

Europol
Daniel DUDEK
Project SYNERGY, Europol, The Hague

EMCDDA
Paul GRIFFITHS
Scientific Director, EMCDDA, Lisbon

Roumen SEDEFOV
Head of unit, Supply reduction and new trends unit, EMCDDA, Lisbon

B. Invited Experts

Dr. Simon ELLIOTT
(ROAR) Forensics Ltd, Worcestershire

Dr. István UJVÁRY
Budapest University of Technology and Economics, Budapest

Dr. David WOOD
Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

C. EMCDDA Staff

Ana GALLEGOS
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Andrew CUNNINGHAM
Scientific analyst, Action on new drugs, Supply reduction and new trends unit

Michael EVANS-BROWN
Scientific analyst, Action on new drugs, Supply reduction and new trends unit

Anabela ALMEIDA
Project assistant, Action on new drugs, Supply reduction and new trends unit

Isabelle GIRAUDON
Scientific analyst, Health consequences, Prevalence, consequences and data management unit

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)

Prepared by: Dr Simon Elliott[a] and Dr Simon Brandt[b]

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Suggested citation: Technical Report on 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25I-NBOMe). EMCDDA, Lisbon, April 2014.

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]) [^{11}C]CIMBI-5. Radiolabelled version (^{11}C on *N*-(2-OCH$_3$)benzyl) used for PET scanning - Center for Integrated Molecular Brain Imaging (CIMBI).

([3]) [^{11}C]CIMBI-5-2. Radiolabelled version with (2-O^{11}CH$_3$) group on phenyl ring also evaluated for PET scanning.

([4]) Radiolabelled *N*-(2-[^{3}H-OCH$_3$]benzyl)-2-[(^{3}H-OCH$_3$] version of 25I-NBOMe ([^{3}H]INBMeO) used as radioligand for binding studies.

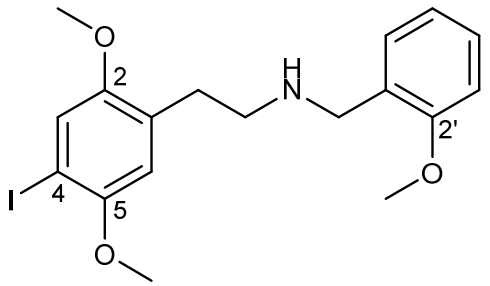
One suggestion for differentiation between these particular isomers was provided recently where the position of the substituent would be explicitly indicated in the abbreviated name which gave, for example, 25I-NB2OMe rather than 25I-NBOMe when referring to *N*-(2-methoxybenzyl) (Casale and Hays, 2012).

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

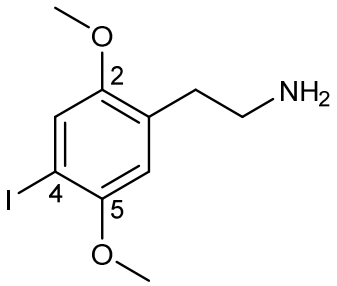
Table 2. Chemical Abstract Service (CAS) Registry Numbers for 25I-NBOMe

CAS Registry Numbers	Variant
919797-19-6	Free base
1043868-97-8	Hydrochloride salt
1248338-50-2	*N*-(2-$^{11}CH_3O$)benzyl free base
1043869-41-5	*N*-(2-C^3H_3O)benzyl free base
1404305-56-1	(2-$^{11}CH_3O$) 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).



25I-NBOMe



2C-I for comparison

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

Molecular weight: 427.28 g/mol (base)

Monoisotopic mass: 427.0644 Da

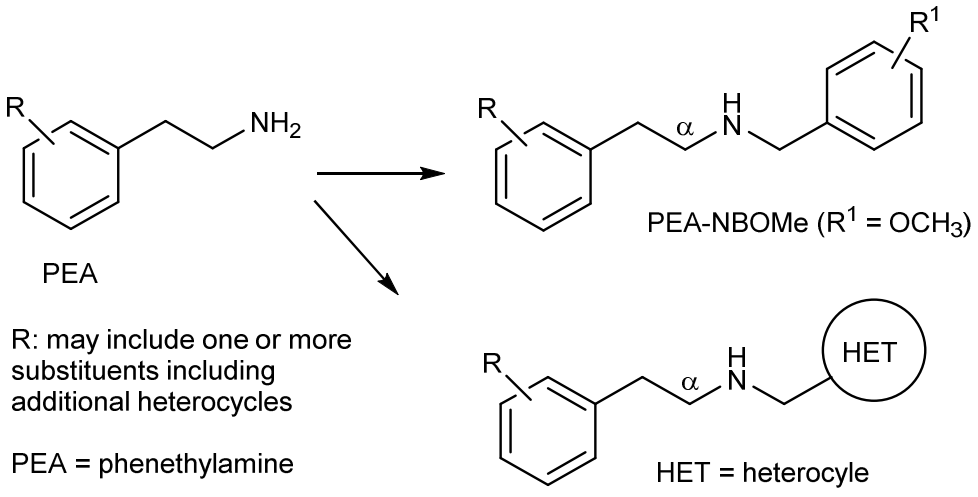
As of 7 March 2014, twelve "NBOMe"-type compounds have been notified to the EU Early Warning System. Nine of them are "NBOMe" analogues in the traditional sense where the amine side chain is connected to the *N*-(2-methoxybenzyl) moiety. One was represented by the dialkylation product (*N*-(2-methoxybenzyl)$_2$) 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 quinazolinedione 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 ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy data (NMR) and electron ionisation (EI) mass spectrum (fragments included $M^{\bullet+}$ 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 $[M+H]^{+}$ 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 (Et_2O/iPrOH·HCl) (Heim, 2003) and 162-166 °C (Et_2O/EtOH·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 $NaBH_4$) 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*-monobenzylation 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 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 µg/kg, i.e. 0.17 µmol/kg) was only slightly less potent than LSD (ED_{50} = 52.9 µg/kg, i.e. 0.13 µmol/kg).

In comparison, 2C-I (ED_{50} = 830 µg/kg, i.e. 2.42 µmol/kg) was observed to be ten-fold less potent than 25-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, CH_3, SEt, Br, CN, SPr, CF_3, 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) (pK_i)
5-HT_{1A}	1696 [a]	-	85	-
5-HT_{1B}	-	-	3742	-
5-HT_{1D}	-	-	-	-
5-HT_{1E}	-	-	-	-
5-HT_{2A}	0.087 [b] 0.044 [c] 0.15 [d]	0.097 [g] 0.15 [h]	2.2 [i] - [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] [^{3}H]8-OH-DPAT as radioligand at h5-HT_{1A}

[b] (±)-[^{125}I]DOI as radioligand at r5-HT$_{2A}$; PI hydrolysis (r5-HT$_{2A}$): EC$_{50}$ 2.50 nM (78% intrinsic activity relative to 5-HT)

[c] (±)-[^{125}I]DOI as radioligand at h5-HT$_{2A}$; PI hydrolysis (h5-HT$_{2A}$): EC$_{50}$ 0.44 nM (81% intrinsic activity relative to 5-HT)

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

[e] (±)-[^{125}I]DOI as radioligand at h5-HT$_{2C}$

[f] (±)-[^{125}I]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 [^{3}H]25I-NBOMe that were labelled by [^{3}H]ketanserin

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

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

[k] [^{3}H]MDL100907 as radioligand at r5-HT$_{2A}$; PI hydrolysis (r5-HT$_{2A}$): ED$_{50}$ 1.02 nM (85% intrinsic activity relative to 5-HT)

[l] [^{3}H]MDL100907 as radioligand at r5-HT$_{2A}$; PI hydrolysis (r5-HT$_{2A}$): ED$_{50}$ 1.02 nM (91% intrinsic activity relative to 10 µM 5-HT)

[m] Hansen: [^{3}H]Ketanserin as radioligand at h5-HT$_{2A}$; PI hydrolysis (h5-HT$_{2A}$): pEC$_{50}$ 9.14 nM (90% intrinsic activity relative to 5-HT). Procedures according to NIMH-PDSP protocols (NIMH-PDSP)

[n] [^{3}H]Mesulergine as radioligand at r5-HT$_{2C}$; PI hydrolysis (h5-HT$_{2C}$): pEC$_{50}$ 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	Strong open and closed eye visuals, including trails, colour shifts, brightening, etc. Mood lift Euphoria Mental and physical stimulation Increase in associative & creative thinking Increased awareness & appreciation of music Life-changing spiritual experiences Erotic, sexual thoughts and sensations Feelings of love and empathy
Neutral	General change in consciousness Pupil dilation Difficulty focusing Unusual body sensations (facial flushing, chills, goosebumps, body energy) Change in perception of time, time dilation Slight increase in heart rate Yawning, especially when coming up Does not suppress appetite

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

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
Values on admission							
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
Clinical features at any time during admission							
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.

	Heart Rate	BP	Seizures?	Intubated?	Urine 25I (ng/mL)	Urine Others
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 e 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.

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