



25I-NBOMe

Report on the risk assessment of 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25I-NBOMe) in the framework of the Council Decision on new psychoactive substances

About this series

EMCDDA Risk Assessments are publications examining the health and social risks of individual new psychoactive substances.

The Risk Assessment Report consists of an analysis of the scientific and law enforcement information available on the new psychoactive substance under scrutiny and the implications of placing it under control. It is the outcome of a meeting convened under the auspices of the EMCDDA Scientific Committee.

This process is part of a three-step procedure involving information exchange/early warning, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

Contents

- 3 | EMCDDA actions on monitoring and responding to new drugs
- 4 | EMCDDA–Europol Joint Report on 25I-NBOMe: a summary
- 5 | Risk Assessment Report of a new psychoactive substance: 25I-NBOMe
- 14 | Annex 1: Technical report on 25I-NBOMe
- 16 | Council Implementing Decision of 25 September 2014 on subjecting 25I-NBOMe, AH-7921, MDPV and methoxetamine to control measures
- 21 | Participants of the risk assessment meeting

Acknowledgements

The EMCDDA would like to thank the following for their contribution in producing this publication:

- | the members of the extended Scientific Committee of the EMCDDA; the advisers to the Scientific Committee and the invited external experts who took part in the risk assessment meeting;
- | the Early Warning System (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
- | the services within each Member State that collected the raw data for the risk assessment;
- | Europol, the European Medicines Agency (EMA) and the European Commission;
- | Dr Simon Brandt and Dr Simon Elliott for preparing the technical review on the pharmacotoxicological, sociological and criminological evidence and public health risks of 25I-NBOMe;
- | Dr Paul Dargan and Dr David Wood for contributing to specific sections of the technical review on 25I-NBOMe;
- | EMCDDA colleagues: Paul Griffiths, Anabela Almeida, Isabelle Giraudon and Katarzyna Natoniewska, who managed the production of the publication.

EMCDDA project leaders: Ana Gallegos, Andrew Cunningham, Michael Evans-Brown and Roumen Sedefov

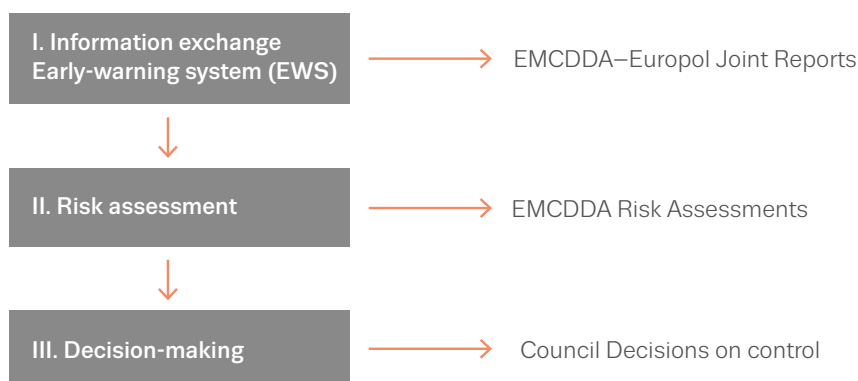
EMCDDA actions on monitoring and responding to new drugs

The EMCDDA has been assigned a key role in the detection and assessment of new drugs in the European Union under the terms of a Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances. It establishes a mechanism for the rapid exchange of information on new psychoactive substances and provides for an assessment of the risks associated with them in order to permit the measures applicable in the Member States for the control of narcotic and psychotropic substances to be applied also to new psychoactive substances.

The three-step process involves information exchange/early warning, risk assessment and decision-making (see below). More detailed information can be found in the section 'Action on new drugs' of the EMCDDA's website:

www.emcdda.europa.eu/activities/action-on-new-drugs

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances



EMCDDA–Europol Joint Report on 25I-NBOMe (2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl) ethanamine) — a summary

EMCDDA–Europol Joint Report on a new psychoactive substance: 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine — in accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

At the end of September 2013, the EMCDDA and Europol examined the available information on a new psychoactive substance 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine, commonly known by the abbreviation '25I-NBOMe', through a joint assessment based upon the following criteria: (1) the amount of the material seized; (2) evidence of organised crime involvement; (3) evidence of international trafficking; (4) analogy with better-studied compounds; (5) evidence of the potential for further (rapid) spread; and (6) evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information available on 25I-NBOMe satisfied criteria 1, 3, 5 and 6. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report on 25I-NBOMe as stipulated by Article 5.1 of the Decision. Accordingly, the NFPs, the Europol national units (ENUs), the EMA and the World Health Organization (WHO) were formally asked to provide the relevant information within six weeks from the date of the request, i.e. by 18 November 2013.

The resulting Joint Report on 25I-NBOMe was submitted to the Council, the Commission and the EMA on 16 December 2013. The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in 25I-NBOMe, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA.

The full text of the Joint Report can be found at:

www.emcdda.europa.eu/publications/joint-report/25I-NBOMe

Risk Assessment Report of a new psychoactive substance: 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25I-NBOMe)

Introduction

This Risk Assessment Report presents the summary findings and 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 that presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion 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 established a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' ⁽³⁾) that may pose a threat to public health and create social problems, including the involvement of organised crime. The Council Decision therefore 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 ⁽⁵⁾.

25I-NBOMe was first identified in a seizure made by Swedish Police in May 2012, and Sweden formally notified the Early Warning System in June 2012. 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 a Joint Report on 25I-NBOMe to the Council of the European Union, the European Commission and the European Medicines Agency (EMA) ⁽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 12 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

⁽¹⁾ EMCDDA (2010), *Risk assessment of new psychoactive substances: operating guidelines*, Publications Office of the European Union, Luxembourg.

⁽²⁾ OJ L 127, 20.5.2005, p. 32.

⁽³⁾ The information exchange mechanism laid down by the Council Decision is operationalised 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 Reitox 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, '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 Schedules 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 Schedules 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.

⁽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.

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 and the other participants attending the risk assessment meeting is included at the end of this publication.

The extended Scientific Committee considered the following information resources during the risk assessment:

- (i) Technical report on 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25I-NBOMe) (Annex 1);
- (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 and grey literature, and Internet drug discussion forums and related websites (hereafter ‘user websites’);
- (iv) data from EMCDDA monitoring of Internet suppliers (which 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 substances. Such information is 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. Some Member States have introduced programmes in the past few years to strengthen these capacities. As a result, more information is available; however, it is likely that serious adverse events remain under-detected.

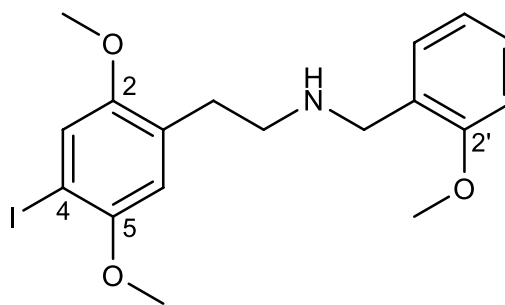
Physical and chemical description of 25I-NBOMe and its mechanisms of action, including its medical value

25I-NBOMe is a ring-substituted phenethylamine substance that is further substituted at the nitrogen atom with a 2-methoxybenzyl moiety (Figure 1). It was invented in the early 2000s. 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.

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

FIGURE 1
The molecular structure, formula, weight, and monoisotopic mass of 25I-NBOMe



Molecular formula: C₁₈H₂₂INO₃

Molecular weight: 427.28 g/mol (base)

Monoisotopic mass: 427.0644 Da

(7) 2-(4-iodo-2,5-dimethoxyphenyl)ethanamine.

(8) EMCDDA (2004), *Report on the risk assessment of 2C-I, 2C-T-2 and 2C-T-7 in the framework of the joint action on new synthetic drugs*, EMCDDA, Lisbon.

(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.)

administration. They 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 and in liquid form. It has been suggested that 25I-NBOMe may be complexed with cyclodextrin to improve buccal absorption; however, to date no analytical confirmation of such a form has been 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). The tentative onset of desired effects is typically reported to be within 15–120 minutes for sublingual/buccal administration, with desired effects lasting 6–10 hours, and within 5–10 minutes for insufflation, with desired effects lasting 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 and liquid chromatography coupled with mass spectrometry 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.

Several *in vitro* and animal studies have investigated the pharmacodynamics of 25I-NBOMe. Vascular and cell-based assays have shown that 25I-NBOMe displays low nanomolar (nM) affinity for the 5-HT_{2A} receptor. In addition, studies on functional activity 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 and clinical observations of individuals who have used 25I-NBOMe suggest that it 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 that 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-HT₆, dopamine D₃, D₄, 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 that 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 have investigated the median lethal dose (LD₅₀) of 25I-NBOMe.

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

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

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

25I-NBOMe is used in scientific research to study the serotonergic system. [¹¹C] 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, ongoing or suspended) for 25I-NBOMe at European Union level or 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.

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 used as a precursor by itself. Once this was formed, a reducing agent (in this case NaBH₄) was employed to yield 25I-NBOMe. Modification of the primary amino group may also include the 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 the 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.

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,

its dependence potential and its similarities to and differences from other chemically or pharmacologically related substances.

It is important to note, when interpreting the information from non-fatal intoxications and deaths reported by the Member States and from clinical case reports and user websites, that individuals may have used other pharmacologically active substances in addition to 25I-NBOMe. The presence of other substances may account for some of 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 from 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 product by Internet retailers and 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 and 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 suggests 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 the 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 re-uptake inhibitors (SSRIs)) and/or substances known to increase serotonin release and/or block re-uptake, which may increase the risk of developing serotonergic toxicity, the symptoms of which can include tachycardia, hypertension, hyperthermia, muscle rigidity and convulsions.

Thirty-two non-fatal intoxications associated with 25I-NBOMe have been reported to the Early Warning System by four Member States: Belgium (three cases), Poland (four), Sweden (18), and the United Kingdom (seven). Fifteen of these have been analytically confirmed.

Four deaths associated with 25I-NBOMe have been reported by three Member States: Belgium (two deaths), Poland (one) and the United Kingdom (one). 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. A report from the United States suggested that a person aged 18 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.

No published animal or human studies 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 the 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 has shown that the composition, including dose, can differ over time and by 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 and in 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 suggests 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 injecting equipment carries the risk of bacterial infections and the transmission blood-borne viruses. Due to the high potency of 25I-NBOMe, the use of powders and liquids may increase the risk of serious adverse events.

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

There are currently no coordinated 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. Some 35.9 % of respondents were from Australia; 33.9 % were from the UK; 17.3 % were from the USA; 10.0 % were from the rest of Europe (excluding the UK); and 2.9 % were from Canada. Most (68.6 %) respondents were male and the mean age was 31.4 (SD = 12.4; range 16–100). Some 2.6 % (n = 582) of respondents reported having ever tried one of the three NBOMe drugs; 25I-NBOMe was the most popular, at 2.0 % (n = 442), 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 had tried it in 2012 and 81.2 % of this group had 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 rest of Europe (excluding the UK), 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 is a popular club drug and that 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 the 2011 European School Survey Project on Alcohol and other Drugs (ESPAD) surveys, with only the Czech Republic reporting a prevalence level of 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.

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 suggests 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, the possibility exists 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.

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

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

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

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. Targeted Internet monitoring by EMCDDA 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.

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 would be subject to evaluation at the 36th meeting of the Expert Committee on Drug Dependence in June 2014.

Article 7.1 of the 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.

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) and 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, the Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, the 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, seven (Austria, Finland, Hungary, the 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 its marketing and production are penalised 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 that, if necessary, is fully applicable.

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

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 the European Union.
- A positive 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 that may also 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 [¹¹C] 25I-NBOMe as a tracer in positron emission tomography imaging studies.
- This control option could create an illicit market in 25I-NBOMe, with an 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.

Conclusion

25I-NBOMe is a ring-substituted phenethylamine substance that 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 Sweden formally notified the Early Warning System in June 2012. 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 people interested in using hallucinogenic substances, including those that have used LSD. However, further information on the size of the demand and the characteristics of these people 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. 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, and 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 that 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 with four 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, the possibility exists 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 of 25I-NBOMe. 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 [¹¹C] 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 is 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 25I-NBOMe has potential positive consequences in terms of reducing its availability and therefore the adverse health and social consequences arising from its use. 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.

ANNEX 1

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

This Technical report was prepared under EMCDDA contract and, while the scientific data presented has been verified to the extent possible, it has not been formally edited by the EMCDDA. The Risk Assessment Report on 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25I-NBOMe), to which this report is annexed was produced by the Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

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

The full text of the Technical report on 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25I-NBOMe) can be accessed under the following link: www.emcdda.europa.eu/publications/risk-assessment/25I-NBOMe/annex1

Table on non-fatal and fatal intoxications, in which 25I-NBOMe was analytically confirmed, has been extracted from the Technical report and is presented in the following pages.

TABLE 7 FROM THE TECHNICAL REPORT

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 (1)	Results for other substances (2)	Notes
Belgium	August 2013	Urine	+	None reported	Lowered consciousness, insufficient breathing, mydriasis, tachycardia (100/min).
Belgium	August 2013	Urine	+	None reported	Lowered consciousness, insufficient breathing, mydriasis, tachycardia (100/min).
Belgium	August 2013	Urine	+	None reported	Headache, lessened strength in 4 extremities, mydriasis, tachycardia (90/min), hypertension (150/85). Symptoms disappeared after being under observation for a couple of hours.
Sweden	2012 – 2013	Not reported	+	None reported	25I-NBOMe detected in five non-fatal intoxications (no further details provided).
United Kingdom	January 2013 (M, 29)	Urine and plasma	+	2C-I, traces of amphetamine and methamphetamine	Severe clinical toxicity. Agitation, aggression, seizures, self-harming behaviour, tachycardia (160/min), hypertension (187/171), tachypnea, oxygen desaturation, pyrexia, rhabdomyolysis. Respiratory and metabolic acidosis, elevation of creatine kinase, impaired renal function. Anuria with a subsequent acute kidney injury. Acute respiratory distress syndrome. Discharged from intensive care unit on day 38, released from hospital on day 43.
United Kingdom	January 2013 (M, 20)	Urine and plasma	+	2C-I, traces of amphetamine and methamphetamine	Severe clinical toxicity. Convulsions (predominantly affecting face), high agitation, poor respiratory effort and clenched jaw. Tachycardia, hypertension, tachypnea, urinary retention, pupillary dilatation, pyrexia, elevated creatine kinase. Visual hallucinations. Released from hospital on day 5.
United Kingdom	January 2013 (M, 20)	Urine and plasma	+	2C-I, traces of amphetamine and methamphetamine	Palpitations, visual hallucinations. Pupillary dilatation, 3 inducible beats of ankle clonus, sinus tachycardia. Discharged on the day of admission.
United Kingdom	January 2013 (M, 20)	Urine and plasma	+	2C-I, traces of amphetamine and methamphetamine	Palpitations, visual and auditory hallucinations. Tachycardia, pupillary dilatation. Discharged on the day of admission.
United Kingdom	January 2013 (M, 19)	Plasma	+	Traces of amphetamine and methamphetamine	Euphoria with visual and auditory hallucinations, violent and agitated behaviour. Discharged after 15 h.
United Kingdom	January 2013 (M, 22)	Plasma	+	Traces of amphetamine and methamphetamine	Nausea and visual hallucinations. Tonic-clonic seizure. Agitated and aggressive behaviour. Creatine kinase elevated. Discharged on the day of admission.
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.
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.

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

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

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

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

Council Decision

COUNCIL IMPLEMENTING DECISION of 25 September 2014 on subjecting 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25I-NBOMe), 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide (AH-7921), 3,4-methylenedioxypropylvalerone (MDPV) and 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) to control measures (2014/688/EU)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances ⁽¹⁾, and in particular Article 8(3) thereof,

Having regard to the proposal from the European Commission,

Whereas:

(1) Risk assessment reports on the new psychoactive substances 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl) phenethylamine (25I-NBOMe), 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide (AH-7921), 3,4-methylenedioxypropylvalerone (MDPV) and 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) were drawn up in compliance with Decision 2005/387/JHA by a special session of the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and were subsequently submitted to the Commission and to the Council on 23 April 2014.

(2) 25I-NBOMe, AH-7921, MDPV and methoxetamine had not been under assessment at the United Nations' level by the time the risk assessment was requested at Union level, but they were evaluated in June 2014 by the Expert Committee on Drug Dependence of the World Health Organization.

(3) 25I-NBOMe, AH-7921, MDPV and methoxetamine have no established or acknowledged medical use (human or veterinary). Apart from their use in analytical reference materials, and in scientific research investigating their chemistry, pharmacology and toxicology as a result of their emergence on the drug market — and, in the case of 25I-NBOMe, also in the field of neurochemistry — there is no indication that they are being used for other purposes.

(4) 25I-NBOMe is a potent synthetic derivative of 2,5-dimethoxy-4-iodophenethylamine (2C-I), a classical serotonergic hallucinogen, which was subject to risk assessment and to control measures and criminal sanctions at Union level from 2003 by Council Decision 2003/847/JHA ⁽²⁾.

(5) The specific physical effects of 25I-NBOMe are difficult to determine because there are no published studies assessing its acute and chronic toxicity, its psychological and behavioural effects, and dependence potential, and because of the limited information and data available.

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

⁽²⁾ Council Decision 2003/847/JHA of 27 November 2003 concerning control measures and criminal sanctions in respect of the new synthetic drugs 2C-I, 2C-T-2, 2C-T-7 and TMA-2 (OJ L 321, 6.12.2003, p. 64).

Clinical observations of individuals who have used this substance suggest that it has hallucinogenic effects and has the potential for inducing severe agitation, confusion, intense auditory and visual hallucinations, aggression, violent accidents and self-induced trauma.

(6) There have been four deaths associated with 25I-NBOMe registered in three Member States. Severe toxicity associated with its use has been reported in four Member States, which notified 32 non-fatal intoxications. If this new psychoactive substance were to become more widely available and used, the implications for individual and public health could be significant. There is no information available on the social risks associated with 25I-NBOMe.

(7) 22 Member States and Norway have reported to the EMCDDA and European Police Office (Europol) that they detected 25I-NBOMe. No prevalence data is available on the use of 25I-NBOMe, but the limited information that exists suggests that it may be consumed in a wide range of settings, such as at home, in bars, nightclubs and at music festivals.

(8) 25I-NBOMe is openly marketed and sold on the internet as a 'research chemical' and information from seizures, collected samples, user websites and internet retailers suggests that it is being sold as a drug in its own right and also marketed as a 'legal' replacement for LSD. EMCDDA identified more than 15 internet retailers selling this substance, who may be based within the Union and China.

(9) The risk assessment report reveals that there is limited scientific evidence available on 25I-NBOMe and points out that further research would be needed to determine the health and social risks that it poses. However, the available evidence and information provides sufficient ground for subjecting 25I-NBOMe to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several reported fatalities, of the fact that users may unknowingly consume it and of the lack of medical value or use of the substance, 25I-NBOMe should be subjected to control measures across the Union.

(10) Since six Member States control 25I-NBOMe under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances, and seven Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles to cross-border law enforcement and judicial cooperation, and would help protect against the risks that its availability and use can pose.

(11) AH-7921 is a structurally atypical synthetic opioid analgesic commonly known by internet suppliers, user websites and media as 'doxylam'. It can be easily confused with 'doxylamine', an antihistaminic medicine with sedative-hypnotic properties, which could lead to unintentional overdoses.

(12) The specific physical effects of AH-7921 are difficult to determine because there are no published studies assessing its acute and chronic toxicity, its psychological, behavioural effects, and dependence potential, as well as the limited information and data available. Based on user reports, the effects of AH-7921 appear to resemble those of classical opioids with the feeling of mild euphoria, itchiness and relaxation; nausea appears to be a typical adverse effect. In addition to self-experimentation with AH-7921, as well as 'recreational use', some of the users report self-medicating with this new drug to relieve pain, others to alleviate withdrawal symptoms due to cessation of the use of other opioids. This may indicate a potential of AH-7921 to spread among the injecting opioid population.

(13) There is no prevalence data on the use of AH-7921, but the information available suggests that it is not widely used, and that when it is used, that use is in the home environment.

(14) 15 fatalities were recorded in three Member States between December 2012 and September 2013 where AH-7921, alone or in combination with other substances, was detected in post-mortem samples. While it is not possible to determine with certainty the role of AH-7921 in all of those fatalities, in some cases it has been specifically noted in the cause of death. One Member State reported six non-fatal intoxications associated with AH-7921. If this new psychoactive substance were to become more widely available and used, the implications for individual and public health could be significant. There is no information available on the social risks associated with AH-7921.

(15) The risk assessment report reveals that there is limited scientific evidence available on AH-7921 and points out that further research would be needed to determine the health and social risks that it poses. However, the available evidence and information provides sufficient ground for subjecting AH-7921 to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several reported fatalities, of the fact that users may unknowingly consume it, and of the lack of medical value or use of the substance, AH-7921 should be subjected to control measures across the Union.

(16) Since one Member State controls AH-7921 under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances and five Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would help protect against the risks that its availability and use can pose.

(17) MDPV is a ring-substituted synthetic derivative of cathinone chemically related to pyrovalerone, which are both subject to control under the 1971 United Nations Convention on Psychotropic Substances.

(18) Information on the chronic and acute toxicity associated with MDPV, as well as on psychological and behavioural effects, and on dependence potential, is not collected uniformly across the Union. Information from published studies, confirmed by clinical cases, suggests that the psychopharmacological profile observed for MDPV is similar to that for cocaine and methamphetamine, albeit more potent and longer lasting. Furthermore, MDPV was found to be 10 times more potent in its ability to induce locomotor activation, tachycardia and hypertension.

(19) Users' websites indicate that its acute toxicity can provoke adverse effects on humans, similar to those associated with other stimulants. These include paranoid psychosis, tachycardia, hypertension, diaphoresis, breathing problems, severe agitation, auditory and visual hallucinations, profound anxiety, hyperthermia, violent outbursts and multiple organ dysfunctions.

(20) 108 fatalities were registered in eight Member States and Norway between September 2009 and August 2013, where MDPV has been detected in post-mortem biological samples or implicated in the cause of death. A total of 525 non-fatal intoxications associated with MDPV have been reported by eight Member States. If this new psychoactive substance were to become more widely available and used, the implications for individual and public health could be significant.

(21) The detection of MDPV has also been reported in biological samples related to fatal and non-fatal road traffic accidents, or driving under the influence of drugs, in four Member States since 2009.

(22) MDPV has been present in the Union drug market since November 2008 and 27 Member States, Norway and Turkey reported multi-kilogram seizures of the substance. MDPV is being sold as a substance in its own right, but it has also been detected in combination with other substances. It is widely available from internet suppliers and retailers, 'head shops' and street-level dealers. There are some indications that suggest a degree of organisation in the tableting and distribution of this substance in the Union.

(23) The risk assessment report reveals that further research would be needed to determine the health and social risks posed by MDPV. However, the available evidence and information provides sufficient ground for subjecting MDPV to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several reported fatalities, of the fact that users may unknowingly consume it, and of the lack of medical value or use of the substance, MDPV should be subjected to control measures across the Union.

(24) Since 21 Member States control MDPV under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances and four Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would protect against the risks that its availability and use can pose.

(25) Methoxetamine is an arylcyclohexylamine substance which is chemically similar to ketamine and the internationally controlled substance phencyclidine (PCP). Like ketamine and PCP, it has dissociative properties.

(26) There are no studies assessing the chronic and acute toxicity associated with methoxetamine, as well as its psychological and behavioural effects, and dependence potential. Self-reported experiences from user websites suggest adverse effects similar to ketamine intoxication. These include nausea and severe vomiting, difficulty in breathing, seizures, disorientation, anxiety, catatonia, aggression, hallucination, paranoia and psychosis. In addition, acute methoxetamine intoxications may include stimulant effects (agitation, tachycardia and hypertension) and cerebral features, which are not expectable with acute ketamine intoxication.

(27) Twenty deaths associated with methoxetamine were reported by six Member States that detected the substance in post-mortem samples. Used alone or in combination with other substances, methoxetamine was detected in 20 non-fatal intoxications reported by five Member States. If this new psychoactive substance were to become more widely available and used, the implications for individual and public health could be significant.

(28) 23 Member States, Turkey and Norway have reported that they detected methoxetamine, since November 2010. Information suggests that it is sold and used as a substance in its own right, but it is also sold as a 'legal' replacement for ketamine by internet retailers, 'head shops' and street-level drug dealers.

(29) Multi-kilogram quantities in powder form were seized within the Union, but there is no information on the possible involvement of organised crime. The manufacture of methoxetamine does not require sophisticated equipment.

(30) Prevalence data are limited to non-representative studies in two Member States. Those studies suggest that the prevalence of the use of methoxetamine is lower than that

of ketamine. The available information suggests that it may be consumed in a wide range of settings, including at home, in bars, nightclubs and at music festivals.

(31) The risk assessment report reveals that further research would be needed to determine the health and social risks posed by methoxetamine. However, the available evidence and information provides sufficient grounds for subjecting methoxetamine to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several reported fatalities, of the fact that users may unknowingly consume it, and of the lack of medical value or use, methoxetamine should be subjected to control measures across the Union.

(32) Since nine Member States control methoxetamine under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances and nine Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would protect against the risks that its availability and use can pose.

(33) Decision 2005/387/JHA reserves to the Council implementing powers with a view to giving a quick and expertise-based response at the Union level to the emergence of new psychoactive substances detected and reported by the Member States, by submitting those substances to control measures across the Union. As the conditions and procedure for triggering the exercise of such implementing powers have been met, an implementing decision should be adopted in order to put 25I-NBOMe, AH-7921, MDPV and methoxetamine under control across the Union,

HAS ADOPTED THIS DECISION:

Article 1

The following new psychoactive substances shall be subjected to control measures across the Union:

- (a) 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl) phenethylamine(25I-NBOMe);
- (b) 3,4-dichloro-N-[[1-dimethylamino) cyclohexyl]methyl] benzamide (AH-7921);
- (c) 3,4-methylenedioxypropylvalerone (MDPV);
- (d) 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine).

Article 2

By 2 October 2015, Member States shall subject in accordance with their national legislation, the new psychoactive substances referred to in Article 1 to control measures and criminal penalties, as provided for under their legislation complying with their obligations under the 1971 United Nations Convention on Psychotropic Substances.

Article 3

This Decision shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

Done at Brussels, 25 September 2014.

For the Council
The President
F. Guidi

Participants of the risk assessment meeting, 1 and 2 April 2014

Scientific Committee members

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- | **Prof. Dr Gerhard Bühringer**, 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 and Psychotherapy, Vienna
- | **Prof. Dr Henk Garretsen**, Faculty of Social and Behavioural Sciences, Tilburg University, LE Tilburg
- | **Prof. Dr Matthew Hickman**, Social Medicine, Bristol
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- | **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

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- | **Dr Peter Blanckaert**, Belgian Early Warning System on Drugs, DO Public Health and Surveillance, Substance use and related disorders (SURD), Brussels
- | **Dr Simon Brandt**, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool
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- | **Prof. Gaetano Di Chiara**, Cagliari University, Biomedical Sciences Department, Cagliari
- | **Dr Dariusz Zuba**, Institute of Forensic Research, Kraków

Representatives of the institutions

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

Invited external 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

EMCDDA staff present

- | **Ana Gallegos**, Head of Sector, Action on new drugs, Supply reduction and new trends unit
- | **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

Recommended citation:

European Monitoring Centre for Drugs and Drug Addiction (2014), *Report on the risk assessment of 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25I-NBOMe) in the framework of the Council Decision on new psychoactive substances*, Risk Assessments, Publications Office of the European Union, Luxembourg.

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The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

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Related publications and websites**EMCDDA**

| Risk assessment of new psychoactive substances — operating guidelines, 2010

EMCDDA and Europol

| EMCDDA–Europol Joint Report on a new psychoactive substance: 25I-NBOMe, 2014

| EMCDDA–Europol 2013 Annual Report on the implementation of Council Decision 2005/387/JHA, 2014

| EMCDDA–Europol Early-warning system on new psychoactive substances — operating guidelines, 2007

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| EMCDDA Action on new drugs website: www.emcdda.europa.eu/drug-situation/new-drugs

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Luxembourg: Publications Office of the European Union
doi: 10.2810/5725 | ISBN 978-92-9168-748-0

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This publication is only available in electronic format.

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