

NBOMe: new potent hallucinogens – pharmacology, analytical methods, toxicities, fatalities: a review

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Abstract. – OBJECTIVE: NBOMe is a class of emerging new psychoactive substances that has recently gained prominence in the drug abuse market. NBOMes are N-2-methoxy-benzyl substituted 2C class of hallucinogens, currently being marked online as "research chemicals" under various names: N-bomb, Smiles, Solaris, and Cimbi. This article reviews available literature on the pharmacology; the analytical methods currently used for the detection and quantification of NBOMe in biological matrices and blotters, together with intoxication cases and NBOMe-related fatalities.

MATERIALS AND METHODS: Relevant scientific articles were identified from Medline, Cochrane Central, Scopus, Web of Science, Science Direct, EMBASE and Google Scholar, through June 2015 using the following keywords: "NBOMe", "Nbomb", "Smiles", "intoxication", "toxicity", "fatalities", "death", "pharmacology", "5-HT_{2A} receptor", "analysis" and "analytical methods". The main key word "NBOMe" was individually searched in association to each of the others.

RESULTS: The review of the literature allowed us to identify 43 citations on pharmacology, analytical methods and NBOMe-related toxicities and fatalities.

CONCLUSIONS: The high potency of NBOMes (potent agonists of 5-HT_{2A} receptor) has led to several severe intoxications, overdose and traumatic fatalities; thus, their increase raises significant public health concerns. Moreover, due to the high potency and ease of synthesis, it is likely that their recreational use will become more widespread in the future. The publication of new data, case reports and evaluation of the NBOMes metabolites is necessary in order to improve knowledge and awareness within the forensic community.

Key Words:

NBOMe, N-Bomb, Pharmacology, Analytical methods, Intoxication, Fatalities.

Introduction

The continual emergence of new psychoactive substances (NPS) is a global issue. Designer drugs, also referred to as bath salts and legal highs^{1,2} include synthetic cannabinoids (Spice), substituted cathinones (e.g., mephedrone, methy-lone, and methylenedioxypropylvalerone (MDPV)) and synthetic hallucinogens (NBOMe, or N-bomb)³. NBOMe class has recently entered the drug scene and is considered to be the newest in a series of designer drugs.

NBOMes are N-2-methoxy-benzyl substituted 2C class of hallucinogens, currently being marked online as "research chemicals" under various names N-bomb, Smiles, Solaris, and Cimbi; originally synthesized for research purposes as potent agonists of 5-hydroxytryptamine receptor subtype 2A (5-HT_{2A})⁴. The 2C hallucinogens (for example: 2C-B, 2C-I, etc.) are phenylethylamines with methoxy group (OCH₃ or OMe) substitutions at the 2- and 5-positions⁵, that possess structure similarities with MDMA and mescaline, causing physical and psychological effects and hallucinations through serotonergic stimulation. The "2C" series of hallucinogenic phenethylamines were first described by Alexander and Anne Shulgin⁶ who used the term "2C" which refers to the two carbons between the benzene ring and the amino group. Chemical structures of phenethylamine, 2C-phenethylamine, 2 C-C and N-(2-methoxybenzyl)-2,5-dimethoxy-4-chlorophenethylamine (25C-NBOMe) are given in Figure 1.

U.S. Drug Enforcement Administration (DEA) ordered an issue to temporary schedule many of the compounds marketed as bath salts in Schedule I status, in October 2011. However, illicit drug designers have demonstrated considerable

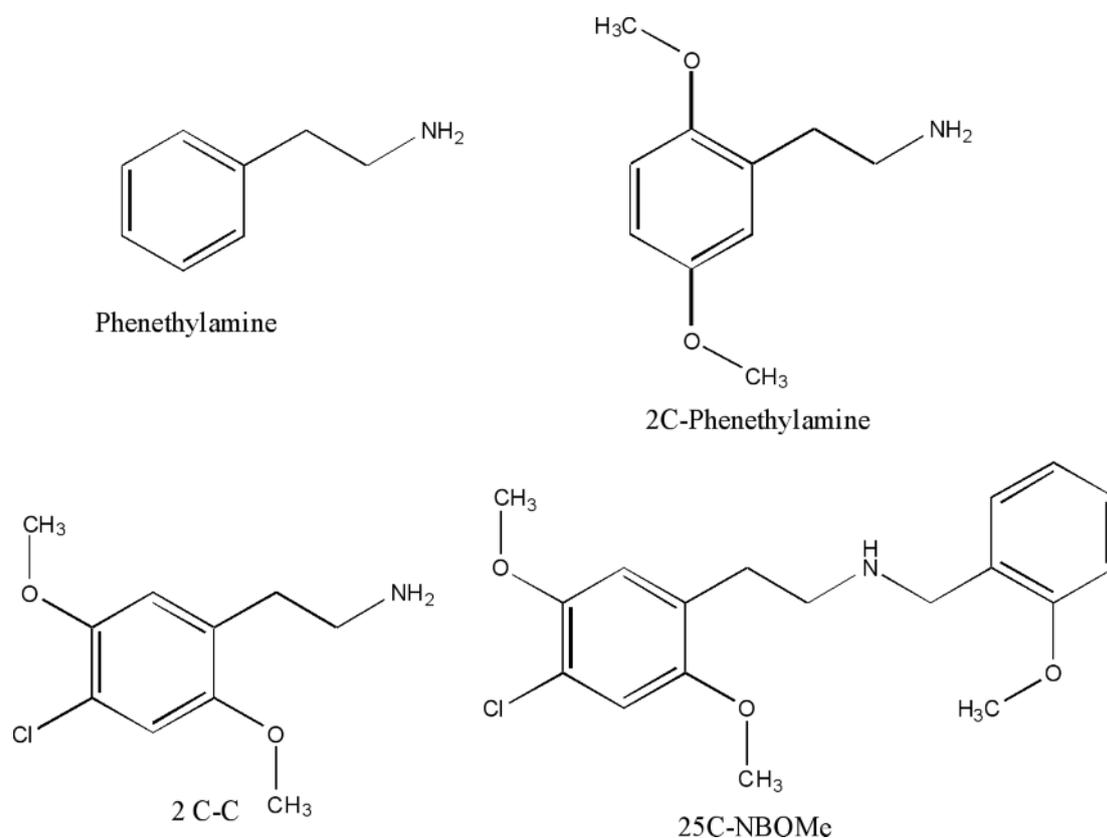


Figure 1. Chemical structures of phenethylamine, 2C-phenethylamine, 2 C-C and 25C-NBOMe.

flexibility in modifying the psychoactive part of designer drugs, which leads to new unscheduled drugs, in order to evade both the legal restriction and detection through analytical methods^{2,7}.

The NBOMe series has practically no history of human consumption prior to 2010 when they first became available on the internet⁸. Blotter papers and powders containing psychedelics appeared on the Polish drug market in 2011 and new phenethylamine derivatives were detected in the Institute of Forensic Research (IFR) in Krakow (Poland). Among others, three representatives of the NBOMe compounds containing alkyl group at position 4 of the benzyl ring⁹ were identified first. Blotter papers impregnated with 25C-NBOMe also entered the market in 2011, and nowadays this drug can usually be found in online shops.

Exemplary blotter papers impregnated with NBOMe compounds that have been analyzed in the State General Laboratory of Cyprus after being seized by the police are presented in Figure 2. The blotters were found to contain a mixture of N-(2-methoxybenzyl)-2,5-dimethoxy-4-

Iodophenethylamine (25I-NBOMe), 25C-NBOMe and 25H-NBOMe.

Substances of NBOMe-class have a high affinity at the 5-HT_{2A} receptor¹⁰, thus sublingual sub-milligram doses may lead to threshold effects^{8,11}. Their effects are likely to be similar to the lysergic acid diethylamide (LSD) and 2C hallucinogens i.e. euphoria, hallucinations, powerful visual and sensory effects, unusual body sensations, mystical experiences, empathic feelings and alterations in consciousness^{11,12}.

Between 2012 and 2013 25 NBOMe exposures were reported to Texas poison centers (USA), 76% involved 25I-NBOMe, 12% 25C-NBOMe, and 12% an unknown NBOMe. The majority (88%) of patients were men and mean age was 17 years (range: 14-25 years)¹³.

Currently, the most widely used NBOMe substances are 25I-NBOMe (street names: 25I, INB-MeO, N-bomb, Smiles, Solaris and Cimbi-5), followed by N-(2-methoxybenzyl)-2,5-dimethoxy-4-bromophenethylamine (25B-NBOMe) and 25C-NBOMe (street names C-Boom, Cimbi-82, Pan-

dora and Dime^{8,14}). Nevertheless, several other drugs belonging to NBOMe class have been indicated in the literature including 2-(2,5-dimethoxy-4-methylphenyl)-N-(2-methoxybenzyl) ethanamine (25D-NBOMe), 2-(4-ethyl-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl) ethanamine (25E-NBOMe), 2-(2,5-dimethoxy-3,4-dimethylphenyl)-N-(2-methoxybenzyl)ethanamine (25G-NBOMe), 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2,3-methylenedioxyphenyl)methyl]ethanamine (25I-NBMD), 25H-NBOMe, 25I-NBF, 25T4-NBOMe, 2CT-NBOMe, 2CBFly-NBOMe, 2CBCB-NBOMe, 25T7-NBOMe, 25TFM-NBOMe, 25T2-NBOMe, 25N-NBOMe and 25P-NBOMe^{4,15,16}.

They are most commonly sold on blotter paper, but they are also available in powder. NBOMe compounds are similarly marketed to LSD i.e. on blotter papers decorated with various artwork patterns. Because of the decreased availability of LSD in recent years, NBOMes are reportedly being sold as LSD or marketed as a “legal LSD”^{8,11}.

25I-NBOMe is available in both powder and liquid form and different ways of intake have been reported including ‘sniffing’, vapor inhalation, oral and intravenous ingestion, while the most common form of administration is sublingual/buccal^{5,14}. Pill ingestion and absorption through oral mucosal route of either the powder form or blotter papers impregnated with the drug has also been reported. It appears to be active at low doses (50-250 µg) and a typical dose ranges from 500 to 800 µg. Anecdotal reports indicate that NBOMes are highly potent when taken sublingually, buccally, or insufflated, but have very low oral bioavailability. Activity time length from 3 to 13 hours has been reported, depending on the route of administration, with the action lasting longer after sublingual administration compared

to insufflation¹⁴. Clinical effects are displayed rapidly after nasal administration and reach a peak 20 minutes after intake. Effects are reported to be similar to those of psilocybin or LSD³. According to users, hallucinations, stimulating effects and depersonalization are displayed after¹⁴.

25C-NBOMe appears to be active at a dose of 200-1000 µg when taken sublingually or intranasally, while doses between 50 and 500 µg when smoked have been reported by users. Light, mild, strong, and very strong effects have been reported after insufflation of 50-200, 200-350, 350-700 and > 700 µg of 25C-NBOMe, respectively. When administered sublingually, the threshold effect is displayed after a dose of 100-250 µg while mild, strong and very strong effects are achieved following 250-450, 450-800 and over 800 µg doses, respectively. Total duration of action can last from 4 to 10 hours⁸.

Even though NBOMes have only been available for a short time, many adverse effects like severe intoxications, traumatic deaths and fatal overdoses have already been documented in case reports. In this paper we aim to review the literature regarding this potent group of NPS and present the available information in pharmacology, even though it is limited and is mostly related to the affinity of this potent group of drugs with the 5-HT_{2A} receptor. Analytical methods for the detection and quantification of NBOMes either in biological samples or blotter papers, analytically confirmed intoxications and NBOMe related fatalities are also presented.

Materials and Methods

Relevant scientific articles were identified from Medline, Cochrane Central, Scopus, Web of



Figure 2. Blotter sheets presenting 3 different artwork patterns containing a mixture of 25I-NBOMe, 25C-NBOMe and 25H-NBOMe. The first (on the left) has dimensions of 19 × 19 cm and is consisted of 900 blotter papers, while the second (in the middle) has dimensions of 6.5 × 6.5 cm and is consisted of 100 blotters. The one on the right is a fragment of a bigger blotter sheet of original size of 19 × 19 cm (900 blotters). Each blotter paper has dimensions of 0.65 × 0.65 cm.

Science, Science Direct, EMBASE and Google Scholar, through June 2015 using the following keywords: “NBOMe”, “Nbomb”, “Smiles”, “intoxication”, “toxicity” “fatalities”, “death”, “pharmacology”, “5-HT_{2A} receptor”, “analysis” and “analytical methods”. The main key word “NBOMe” was individually searched in association to each of the others.

Results

The review of the literature allowed us to identify 43 citations^{3,6,8,46} on pharmacology, analytical methods and NBOMe-related toxicities and fatalities. The findings are below discussed.

Pharmacology

There is limited information on pharmacological data concerning NBOMe series. Psychopharmacology (i.e. effects on consciousness and hallucinations) of psychedelic substances including LSD is attributed to the agonist action on the serotonin 5-HT_{2A} receptor^{9,17}. The 5-HT_{2A} receptor has been associated with complex behaviors including cognitive processes and working memory and it is also involved in the pathophysiology of affective disorders such as schizophrenia and depression.

Structure-activity relationship (SAR) studies have led to substances with low nanomolar affinities for this specific receptor, some of which are among the most potent partial agonists with hallucinogenic effects known to date¹⁸⁻²¹. Data suggest that drugs of 2C-class interact effectively with serotonin receptors, most of which act as 5-HT_{2A} receptor agonists. Typically, a 2C-class substance carries a lipophilic substituent in the para position (relative to the side chain), which contributes to further enhance 5-HT_{2A} affinity and partial agonistic action^{22,23}. The most active compounds identified to date possess an ether, alkylthio, alkyl, or halogen group at this position and their potency increases in the aforementioned sequence^{24,25}. The results retrieved from SAR studies suggest that N-substitution of common phenethylamines with short alkyl substituents (methyl or ethyl groups) considerably decreases the binding affinity for serotonin receptors compared to the unmodified compounds. However, the addition of an N-benzyl moiety increases the affinity and potency⁴. Braden et al²⁶ illustrated this by adding an N-benzyl group to 2,5-dimethoxy-b-phenethylamine (2C-H); the

binding affinity increases 13-times²⁶. The addition of an N-(2-methoxy) benzyl, or N-(2-hydroxy) benzyl, group to 2C-H led to 190- and 82-fold increases in affinity, respectively. Moreover, the latter substances displayed high selectivity (> 1000-fold) for 5-HT_{2A} receptors over 5-HT_{1A} and moderate selectivity (up to 35-fold) for 5-HT_{2A} over 5-HT_{2C}.

Subsequently, Silva et al²⁷ studied a series of 51 arylethylamines (indoles, methoxybenzenes, and quinazolinones), partial agonists of 5-HT_{2A} and concluded that among the substituents at the amino nitrogen, a 2-methoxybenzyl group was the most favorable.

Heim²⁸ was the first to investigate the pharmacological properties of NBOMe-series. 25C-NBOMe acts as a potent 5-HT_{2A} receptor's partial agonist. 11C radiolabeled form of 25C-NBOMe has been studied as a potential ligand to map the distribution of 5-HT_{2A} receptors in the brain by positron emission tomography (PET)¹⁵. This drug has a nanomolar affinity to the 5-HT_{2A} receptor displaying an agonistic binding affinity of 2.89 ± 1.05 nM *in vitro*¹⁵ thus it has been characterized as “superpotent” by Braden et al⁴. It is pharmacologically active even at considerably small submilligram doses⁸.

Moreover, Halberstadt and Geyer¹⁰ studied the effects of 25I-NBOMe on the head twitch response (HTR) that is induced by activation of 5-HT_{2A} receptor in rats and mice and is widely used as a behavioral proxy for hallucinogen effects in humans. 25I-NBOMe displayed 14-fold higher potency than 2C-I. The findings suggest that phenethylamine hallucinogens induce the HTR by activating 5-HT_{2A} receptors and that 25I-NBOMe is a highly potent derivative of 2C-I, which is in accordance to previous *in vitro* findings suggesting that N-benzyl substitution increases 5-HT_{2A} affinity.

Presently, there is limited information regarding the metabolic pathways of NBOMe compounds. Stellpflug et al²⁹ analyzed a urine sample, collected from a 25I-NBOMe intoxicated subject, in order to establish the metabolism of the drug by identifying excreted metabolites. The sample was collected approximately 3 h after exposure to the drug. At that point, unchanged 25I-NBOMe was detected along with a single demethylated metabolite that was found at a level approximately 80-fold higher than the parent drug. Another demethylated product was also detected at levels similar to those of the unchanged compound. All of the demethylated metabolites

were found to be excreted exclusively as glucuronide conjugates. 25H-NBOMe and 2C-I were also detected, although their use was not reported. More likely, 25H-NBOMe was present as a contaminant in the ingested drug formulation. The presence of 2C-I could be explained as 25I-NBOMe is most commonly synthesized by the reductive coupling of methoxybenzaldehyde with 2C-I or 2C-I could result from metabolic cleavage of 25I-NBOMe at the amine within the chain linking of the two ring structures.

Analytical Methods

Although laboratory testing is expanding in order to include the so called new designer drugs, widespread standardized testing targeting these drugs is not yet available in most forensic and clinical toxicology laboratories. A number of methods to identify and quantify NBOMe compounds in biological specimens have been reported in literature. The most commonly reported chromatographic separation techniques for this purpose is either high performance liquid chromatography (HPLC) or ultra-performance liquid chromatography (UPLC) coupled to either tandem mass spectrometry (MS-MS) or high-resolution time-of-flight mass spectrometry (HRTOF-MS). As extraction procedure both liquid-liquid extraction (LLE) and solid phase extraction (SPE) have been stated. Poklis et al³⁰ developed a HPLC/MS/MS method for the identification and quantification of 25I-NBOMe and 2CC-NBOMe in the serum of intoxicated subjects. The samples were extracted using SPE technique and 25H-NBOMe was used as internal standard. In a subsequent study³¹ a HPLC-MS-MS method for the detection and quantification of nine NBOMe compounds in urine (25H-NBOMe, 25C-NBOMe, 25I-NBF, 25D-NBOMe, 25B-NBOMe, 2CT-NBOMe, 25I-NBMD, 25G-NBOMe and 25I-NBOMe) using a rapid SPE was developed. Moreover, HPLC-MS/MS method for the identification and quantification of 25B-NBOMe in serum and urine, after a simple LLE technique using 25H-NBOMe as the internal standard was developed and then applied in a severe intoxication case³².

Identification of 25C-NBOMe and a demethylated and glucuronidated metabolite of 25C-NBOMe in urine and blood samples was achieved by using UPLC-HRTOF-MS, while quantification of this potent drug in post-mortem specimens (peripheral whole blood, urine, vitre-

ous humor, liver, and gastric content) and in ante-mortem whole blood sample was performed by UPLC-MS/MS³³. Stellpflug et al²⁹ used LC-MS/MS for the quantification of 25I-NBOMe and UPLC-TOF-MS for the identification of excreted metabolites of the same drug in urine samples collected from a clinical case. Pasin et al³⁴ developed and validated a method for the detection and identification of 37 new designer drugs, including 25B-NBOMe, 25C-NBOMe, 25H-NBOMe and 25I-NBOMe, in whole blood using LC-QTOF-MS.

Blotter paper is among the most common means of administration of the so called NBOMe compounds. Forensic analysis of blotters is normally performed by GC-MS or LC-MS^{8,35}. The latest techniques require a sample preparation, including extraction of analytes by soaking blotters in organic solvents, filtration and/or dilution, prior to injection which, however, is considered to be time consuming and sample-destructive. Coelho³⁶ reported a method that rapidly detects NBOMes and other NPS by taking ATR-FTIR spectra directly from the blotters. In 39 blotter papers tested (out of 77) three types of NBOMe class (25B-NBOMe, 25C-NBOMe and 25I-NBOMe) were detected. This analysis should only be considered as a quick preliminary test since each blotter is a mixture of paper and one or more NPS, which reduces the discriminating power of IR spectrometry, therefore confirmation with analytical techniques such as GC-MS or LC-MS is still necessary.

NBOMe Related Toxicities

NBOMe series have been implicated in severe clinical intoxications, with patients commonly displaying serotonergic and sympathomimetic symptoms. Such intoxications have been reported not only in media³⁷ and internet forums but also in scientific literature, providing information on the effects produced after the administration of these potent compounds and the concentrations in biological fluids. A comprehensive review by Suzuki et al³⁸ has recently been published, putting together the published reports of NBOMe-linked toxicities, providing demographic and clinical data and information on adverse effects. However, here emphasis is given to the circumstances of each case separately and the concentrations found in biological samples.

Suzuki et al¹¹ reported a case of attempted suicide after 25I-NBOMe ingestion. An 18

year-old male had sublingually taken two “blotters” claimed to be “good LSD”. One hour after the ingestion he began to experience euphoria, tachycardia, and visual hallucinations. After several hours the drug effects continued to increase in intensity and the man displayed anxiousness and confusion. Then feeling trapped, he became anxious and began to panic; in order to end this experience he attempted to commit suicide using a pair of scissors stabbing himself in the neck and chest. When he realized the extent of his injuries, approximately 11 hours after drug intake he called the emergency services. His symptoms were treated at the emergency unit and he was sent to the operating room for wound exploration and closure. Three days after admission, he was transferred to a psychiatric facility for continued treatment and was finally discharged a week later.

Hill et al³⁹ described the effects produced in 7 young adult males after analytically confirmed recreational use of 25I-NBOMe in the United Kingdom. Tachycardia and elevated creatine kinase were displayed in all 7 cases, while 6 out of 7 patients showed agitation, aggression, visual and auditory hallucinations. Hypertension was noticed in 4 subjects, while in 3 cases the clinical features included seizures, hyperpyrexia and metabolic acidosis. Clonus and elevated white cell count were noticed in 2 individuals while in one case there was acute kidney injury. The authors concluded that severe clinical toxicity may occur after recreational intake of this potent drug, with serotonergic and stimulant features predominating.

According to Rose et al⁴⁰, an 18-year-old male was suffering with severe agitation, hallucinations, tachycardia and hypertension. Serum sample, collected during emergency department evaluation, was found to contain 0.76 ng/ml of 25I-NBOMe. Although, the patient’s symptoms gradually improved leading him to recover over a period of 48 hours, he continued to suffer from episodes of aggressiveness. Another case involving an 18-year-old female with tachycardia, agitation, hypertension, confusion and seizure is described by Stellpflug et al²⁹. In this case the 25I-NBOMe urine level was 7.5 ng/mL and 25H-NBOMe was also detected. She improved after benzodiazepine administration and was discharged 7 hours post-ingestion²⁹. Poklis et al³⁰ reported two severely intoxicated cases with serum 25I-NBOMe concentrations of 250 and 2780 pg/mL.

A 19-year-old man was in danger of dying after nasal intake of 2 mg of 25C-NBOMe. Two hours after administration, he experienced a generalized seizure, loss of consciousness and low oxygen saturation thus mechanical ventilation was required. On day 2, he appeared to recover quickly but he developed acute kidney failure requiring hemofiltration on the third day. Acute lung failure developed on day 4, while on days 7 and 8 his condition became life threatening due to insufficient oxygenation. Finally he fully recovered after 13 days in the intensive care unit⁴¹. A 24-year-old female, after analytically confirmed ingestion of 3 blotters containing 25C-NBOMe and a smaller amount of 25I-NBOMe had the following symptoms: tachycardia, tachypnea, agitated delirium, confusion, impression of being attacked, dilated pupils and disorientation³⁵.

A serum and urine 25B-NBOMe concentrations of 180 pg/ml and 1900 pg/ml, respectively were determined after a 19-year-old male was found unresponsive with generalized grand mal seizure activity, following the administration of an unknown drug, called 25B³². In another two cases reported by Tang et al⁴² two male patients of 17 and 31 years displayed the same features as above described by Rose et al⁴⁰, following an ingestion of drugs labelled as ‘NBOMe’, together with confusion, hyperthermia, sweating, dilated pupils, convulsion, rhabdomyolysis and deranged liver function. 25B-NBOMe was identified in both urine samples, whereas 25C-NBOMe was detected in one of the urine samples.

Table I illustrates the NBOMe concentrations found in patients suffering from toxicity after intake of NBOMe compounds together with the route of administration, product and dose consumed and other toxicological findings. In this table only those reports providing quantification of NBOMe substances in biological samples, have been included^{11,29,32,40,43}.

NBOMe Related Deaths

NBOMe compounds, although only recently encountered in the drug market, have already been associated with a number of fatalities mainly reported in the so-called grey literature, including personal drug experience websites, newspapers and internet forums. However, only four papers, representing 5 cases, have been published providing information on analytically confirmed NBOMe-related deaths^{33,44-46}. The findings of these 4 papers are here provided.

Table 1. Concentrations found in biological samples after NBOMe toxicity, in published reports.

Study/Year/Reference	Age/Gender	Route of administration/dosage/product consumed	Analytically confirmed NBOMe compound(s)	Quantitative analysis of NBOMe compounds	Other substances
Kelly et al ⁴³	18-19/M	Mouth ingestion or insufflation/Unknown/25I-NBOMe	25I-NBOMe	Urine conc. : 2 ng/mL	Caffeine
	18-19/M	Mouth ingestion or insufflation/Unknown/25I-NBOMe	25I-NBOMe	Urine conc. : 36 ng/mL	Caffeine
	18-19/M	Mouth ingestion or insufflation/Unknown/25I-NBOMe	25I-NBOMe	Urine conc. : 28 ng/mL	Caffeine and nicotine
Rose et al ⁴⁰	18/M	Unknown/Unknown/25I-NBOMe	25I-NBOMe	Serum concentration: 0.76 ng/mL	THC
	18/F	Sublingual/Unknown/25I-NBOMe	25I-NBOMe, 25H-NBOMe, and 2C-I	Urine concentration: 25I-NBOMe:7.5 ng/mL 25H-NBOMe: 0.9 ng/mL 2C-I: 1.8 ng/mL	Not-reported
Suzuki et al ¹¹	18/M	Sublingual/2 hits/LSD	25I-NBOMe	Serum concentration: 0.034 ng/mL	THC
	19/M		25B-NBOMe	Serum concentration: 0.180 ng/mL	THC
Poklis et al ³⁰	Not-reported	Unknown/Unknown/25I-NBOMe	25I-NBOMe	Urine concentration: 1.9 ng/mL	Not-reported
	Not-reported		25I-NBOMe	Serum concentration: 0.25 ng/mL Serum concentration: 2.78 ng/mL	Not-reported

Poklis et al⁴⁴ presented a traumatic fatality of a young (19 years-old) man who had ingested blotter paper containing 25I-NBOMe. After ingestion this man displayed paranoid behavior and he was finally found by his friends unresponsive on the pavement near the apartment complex swimming pool. It is believed that the deceased had either jumped or had fallen from his balcony located multiple floors above where he was found. It is worth pointing out that although the decedent had ingested the same drug as his friends, he was the only one to display bizarre behavior, probably because this was the first time he had ingested a hallucinogenic drug.

Toxicological analysis of biological fluids and tissues retrieved the following results: peripheral blood, heart blood, urine, vitreous humor, gastric contents, bile, brain and liver 405 pg/mL, 410 pg/mL, 2.86 ng/mL, 99 pg/mL, 7.1 µg total, 10.9 ng/g, 2.54 ng/g and 7.2 ng/g, respectively.

Since the urine and blood concentrations found in this postmortem case fall within the range of values of the 25I-NBOMe intoxicated patients reported in literature, authors assume that the deceased was suffering from mental confusion and/or delusional thoughts and/or hallucinations which possibly contributed to his fall, whether intentional, i.e. commit suicide or attempt to fly, or accidental⁴⁴.

Kueppers and Cooke⁴⁵ reported a fatal case where three NBOMe compounds were detected in the post mortem aortic non-preserved blood and urine. The deceased (23 year-old woman) was witnessed sniffing an unknown white powder. After nasal intake she demonstrated strange behavior, agitation and began uttering random words, shouting, and eventually started thrashing about aggressively. After going into a seizure and vomiting she collapsed and was pronounced dead.

25I-NBOMe, 25H-NBOMe and 25C-NBOMe were present in post-mortem blood at approximate concentrations of 28, 1 and 0.7 µg/L, respectively. In this case the level of 25I-NBOMe found in blood appears to be much higher than that previously reported in intoxicated patients and analytically confirmed 25I-NBOMe-linked fatalities. Moreover, methylamphetamine (0.39 mg/L), tetrahydrocannabinol (3.4 µg/L) and a small amount of promethazine were also detected in the decedent's blood thereby determining the cause of death to be a combined drug toxicity including 25I-NBOMe⁴⁵.

Andreasen et al³³ reported a fatal overdose case involving 25C-NBOMe. A young man pronounced dead at hospital approximately 12h after the recreational use of this compound. Both ante- and post-mortem samples were collected and analyzed. Analysis of ante-mortem whole blood, collected at 2-4 hours after ingestion of the drug, retrieved a 25C-NBOMe concentration of 0.81 µg/kg. In the post mortem samples, peripheral whole blood, urine, vitreous humour, liver and gastric content, the drug was found at the following concentrations: 0.6, 2.93, 0.33, 0.82 µg/kg and 0.32 µg total, respectively.

The cause of death was attributed to a fatal overdose of 25C-NBOMe in combination with amphetamine intake. Again, although the deceased had sniffed the drug with a friend of his, the friend displayed none of the symptoms that the decedent had i.e. strange behavior, hallucinations and jerky movements but he only reported having “a good trip” for 4-6 h after ingesting the 25C-NBOMe³³.

Moreover, Walterscheid et al⁴⁶ also cited 2 deaths after 25I-NBOMe ingestion, in both cases the cause of death was attributed to fatal 25I-NBOMe toxicity. However, no quantification results are given⁴⁶.

A summary of the findings (both autopsy and toxicological) of the four papers above described is given in Table II.

Discussion

NBOMe is a novel dangerous group of hallucinogenic drugs which has recently gained prominence. Although this potent group of drugs was first synthesized for scientific purposes as a tool to study the 5-HT_{2A} receptor, it is currently used as a recreational drug. It can be assumed that these pharmacological studies have attracted the interest of clandestine designers of NPS.

The fact that this class of drugs is being counterfeited as LSD raises significant health concerns, since a recreational LSD user may consume NBOMe unintentionally. In fact, both in severe intoxications and fatal cases where the ingestion of NBOMe compounds was analytically confirmed the individuals involved, incorrectly thought they had consumed “acid”^{11,35,44,46}. The effects produced after the use of “traditional” hallucinogens, including LSD, are treated with the use of benzodiazepines. Moreover, no fatal cases attributed to LSD overdose have been re-

ported⁴⁷. In contrast, despite the fact that NBOMes have only recently entered the drug market scene a number of severe intoxications and deaths have been linked to this group. Thus, medical and paramedical personnel are encouraged, when managing patients who present symptoms of psychosis and are presumed to be drug abusers or report recent use of LSD or other hallucinogens, to consider the diagnosis of an inadvertent NBOMe-type drug overdose therefore taking all the necessary precautions needed³⁷.

Results obtained by Coelho³⁶ suggest great inhomogeneity in drug dosages even within blotters presenting the same artwork, taken from the same blotter sheet. This could be attributed to the fact that these drugs are produced in clandestine labs by amateur cooks⁵. Taking into account the potency of this class, the variation of purity and the inhomogeneity in drug dosages users can easily overdose.

Moreover, the high potency and small dose ingested makes analytical detection of NBOMes exceedingly difficult. Even for laboratories with highly sensitive methods the detection of these hallucinogens is challenging, since the signals from these drugs are very low and are easily lost in the background noise of the sample. Therefore, it is worth pointing out that it is of the utmost importance for clinicians, forensic pathologists and investigators in intoxication and fatal cases to provide relevant information and circumstances of their cases to the toxicology laboratory. Moreover, due to the lack of proper routine analytical methods, the number of NBOMe related intoxications and fatal cases may well be underestimated.

Furthermore, although 3 representatives of this potent class have been temporarily scheduled in schedule 1 of the Controlled Substances Act by DEA (Drug Enforcement Administration), further legislative measures should be taken worldwide since these drugs are only banned in some countries.

Conclusions

Due to the high potency and ease of synthesis, it is likely that the recreational use of NBOMe will become more widespread in the future. The publication of new data, case reports and evaluation of the NBOMes metabolites is necessary in order to improve knowledge and awareness within the forensic community.

Table II. NBOMe-related fatalities. Circumstances of death, autopsy and toxicological findings.

Study/Year	Age/ Gender	Case circumstances	Autopsy findings	NBOMe concentration	Other toxicological findings	Cause of death
Kueppers and Cooke/2015 ⁴⁵	23/F	-Witnessed nasally insufflating an unknown substance (a white powder), -Shortly after drug intake she began acting strangely, uttering random words, appearing agitated, shouting, and eventually started thrashing about aggressively -Seizing, vomiting -Collapse and death.	Multiple fresh-appearing superficial bruises and abrasions -Heavy and congested lungs	25I-NBOMe concentrations Post mortem aortic non-preserved blood: 25I-NBOMe: 28 µg/L 25H-NBOMe: 1 µg/L 25C-NBOMe: 0.7 µg/L	Preserved mortuary admission blood: methylamphetamine: 0.39 mg/L tetrahydrocannabinol: 3.4 µg/L -promethazine	combined drug toxicity including 25I-NBOMe
Poklis et al/2014 ⁴⁴	19/M	-Ingested blotter paper infused with "acid" (either knowingly or unknowingly) -Began to display strange and paranoid behavior -Abruptly walked away from his friends - Found prone and unresponsive near his apartment complex swimming pool pronounced dead - had either jumped or had fallen accidentally from his apartment balcony (according to police and paramedics)	-Multiple blunt impact injuries, including lacerations of the heart, aorta, liver and spleen. -The skull had multiple fractures of the calvarium and base, with subdural and subarachnoid hemorrhages, cortical contusions and traumatic axonal injury. - a piece of paper (1.4 cm x 0.6 cm x 0.1 cm) was found in stomach contents and was submitted for analysis	25I-NBOMe concentrations Peripheral blood: 405 pg/mL heart blood: 410 pg/mL urine: 2.86 ng/mL vitreous humor: 99 pg/mL gastric contents: 7.1 µg total bile: 10.9 ng/g brain: 2.54 ng/g liver: 7.2 ng/g.	None	-skull fractures with contusions of brainstem and lacerations of heart and aorta due to blunt impact to head and torso (fatal behavioral intoxication due to ingestion of 25I-NBOMe)

Table continued

Table II. (Continued). NBOMe-related fatalities. Circumstances of death, autopsy and toxicological findings.

Study/Year	Age/ Gender	Case circumstances	Autopsy findings	NBOMe concentration	Other toxicological findings	Cause of death
Andreasen et al/2015 ³³	22/M	<ul style="list-style-type: none"> - recreational use of 25C-NBOMe (nasal ingestion) - hallucinations, jerky movements and clenched jaw -hospitalization - unconsciousness - lifesaving treatment - pronounced dead at hospital at approximately 12 h after ingestion 	<ul style="list-style-type: none"> -minor external injuries (superficial bruises and abrasions) -organ congestion, with free fluid in thorax and abdomen -diffuse mucosal hemorrhage, especially in the lower parts of the colon -histopathology: degeneration of the liver 	<p>25C-NBOMe concentrations</p> <p>1. Postmortem samples: peripheral whole blood: 0.60 µg/kg urine: 2.93 µg/kg vitreous humor: 0.33 µg/kg liver: 0.82 µg/kg gastric content: 0.32 µg total</p> <p>2. Ante-mortem samples: whole blood: 0.81 µg/kg</p>	<p>1. Postmortem blood: Amphetamine: 470 µg/kg THC: 1.5 µg/kg 11-nor-9-Carboxy-THC: 8.9 µg/kg Quetiapine: 13 µg/kg Amitodarone: 120 µg/kg Acetaminophene: 5000 µg/kg Diazepam: 99 µg/kg Demethyl/diazepam: 12 µg/kg Fentanyl: 0.47 µg/kg Ketamine: 120 µg/kg Lidocaine: 78 µg/kg Midazolam: < 6 µg/kg</p> <p>2. Ante mortem blood: Amphetamine: 370 µg/kg</p>	<p>Fatal overdose of 25C-NBOMe in combination with amphetamine intake.</p>
Walterscheid et al/2014 ⁴⁶	<p>Case 1: 21/M</p> <p>Case 2: 15/F</p>	<p>Case 1:</p> <ul style="list-style-type: none"> -Attended a rave party -Took "acid" -smoked marijuana -sudden violent behavior -hallucinations -became unresponsive -pronounced dead at the scene <p>Case 2:</p> <ul style="list-style-type: none"> -socializing outside a rave party -ingested an unknown clear liquid -became ill -rapidly deteriorated as her friend transported her to the hospital. -became unresponsive -taken to hospital -lifesaving attempts -pronounced dead 	<p>Case 1:</p> <ul style="list-style-type: none"> -numerous external injuries that were consistent with physical aggression <p>Case 2:</p> <ul style="list-style-type: none"> -external contusions 	<p>Case 1:</p> <p>25I-NBOMe</p> <p>Case 2:</p> <p>25I-NBOMe</p>	<p>Case 1:</p> <p>marijuana</p> <p>Case 2:</p> <p>marijuana</p>	<p>Case 1:</p> <ul style="list-style-type: none"> -fatal 25I-NBOMe toxicity <p>Case 2:</p> <ul style="list-style-type: none"> -fatal 25I-NBOMe toxicity,

Conflict of Interest

The Authors declare that they have no conflict of interests.

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