OBSERVATOIRE FRANÇAIS DES DROGUES ET DES TOXICOMANIES

trend
Internet tools for research in Europe on new drugs

"25*x*-NBOMe" type molecules

Available information on the diffusion of a class of NPS in France

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INTRODUCTION

This document summarises the available data on the 25x-NBOMe molecule group.

25*x*-NBOMe, or NBOMe, constitute a group of compounds (25I-NBOMe, 25B-NBOMe, etc.) belonging to the phenethylamines family[1], which mainly has psychedelic effects[2]. These molecules are new psychoactive substances (NPS). Their diffusion has strongly increased over the past decade (Lahaie *et al.*, 2013). These substances can have a much longer action duration than LSD, and are often sold and used as a substitute for the latter. 25I-NBOMe appears to be the most widely used compound in this group.

This summary was drawn up based on the OFDT survey and monitoring schemes (TREND and SINTES network, I-TREND project[3]), available data collected from the EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) and the national institutions working in the field of drugs, whether in the health sector (ANSM addiction monitoring, CAP-TV network, *Santé Publique France*, SFTA[4]) or in the law enforcement sector (SCL and INPS[5]).

By investigating the history of the emergence of these compounds, this summary will first endeavour to explain how 25*x*-NBOMe gained a foothold in the French market, and will then describe in detail the potential and limits of their diffusion before examining the challenges inherent in their presence.

1. Its chemical structure is modelled on the molecules which symbolise this class, namely MDMA, amphetamines or even 2C-B. It has stimulant, empathogenic and, to varying degrees, hallucinogenic properties.
2. So-called hallucinogenic substances are usually divided into sub-groups, according to the main effect. Several classifications exist. Psychedelic molecules are particularly characterised by hallucinations (visual, audible, etc.), by changes in the perception of self and of the world, or by introspective experiences.
3. Internet Tools for Research in Europe on New Drugs, JUST/2012/DPIP/AG/3641, co-funded by the European Union.
4. French National Agency for Medicines and Health Products Safety, Poison Control and Toxicovigilance Centre, French Public Health Agency, French Society of Analytical Toxicology.
5. Customs Joint Laboratories Department (Paris site), French National Forensic Science Institute (Lyon site).

EMERGENCE AND ESTABLISHMENT OF 25*x*-NBOME

25*x*-NBOMe substances appeared on the online (Internet) market around 2010 and were rapidly experimented by a specific user sub-group, the e-psychonauts[6].

2013-2014: COMMERCIAL SPREADING

In 2013, 25*x*-NBOMe began to be sold on the "real" market[7] and collected via the SINTES network, in new, rare forms, with invented names such as "Vortex". Its diffusion then reached far beyond those who exclusively purchase on the Internet. In 2014, all TREND site coordinators stated that this type of substance was visible in private[8] or public recreational settings[9] (Cadet-Taïrou *et al.*, 2014). During this diffusion phase, 25*x*-NBOMe were perceived ambivalently by users, attracting relative interest while considered dangerous. It was during this period that practically all serious adverse events with major health complications were recorded in France (see "Health signals reported to the monitoring schemes", p. 18).

2015: CONTROL OF THE 25*x*-NBOMe AND ADAPTATION OF SUPPLY TO USER HABITS

From late 2014 - early 2015, 25*x*-NBOMe were less frequently described by invented names. They were more often designated by ambiguous names (i.e. “synthetic LSD” or “synthetic mescaline”), then increasingly directly as LSD (Cadet-Taïrou *et al.*, 2015). During this period, drug dealers attempted to mirror user habits, by playing on the names and possible forms. Their choices illustrate the way in which they adapt the supply to an audience still "traditional" in its consumption choices.

In 2015, while several 25*x*-NBOMe compounds were controlled during the year, it became more difficult to formally confirm their presence on the market (Cadet-Taïrou *et al.*, 2016). Divergent information is available according to the different sources and geographical locations to indicate that drug dealing markets are emerging in the local real-life (see " Since 2014, a swing towards micro-trafficking", p. 13). While users described experiences clearly characteristic of these compounds, in terms of their duration and intensity, the number of noteworthy health signals and freight seizures has decreased.

6. Psychonautism involves attempting to modify brain activity using psychoactive substances or physical techniques (meditation, trance, etc.), in the belief that this altered state allows greater insight into personal psychology or communication with a divine or spiritual entity.
7. i.e. the face-to-face market, where the buyer and seller meet.
8. i.e. private parties which usually take place in the home.
9. The recreational setting defined by TREND is initially centred on the techno scene, i.e. venues where events based on this music trend take place. It encompasses the so-called alternative scene (free parties, teknivals, and alternative areas within more general festivals, etc.), as well as commercial or conventional settings (clubs, discos and music bars). It is tending to spread towards the general recreational setting and even private parties.

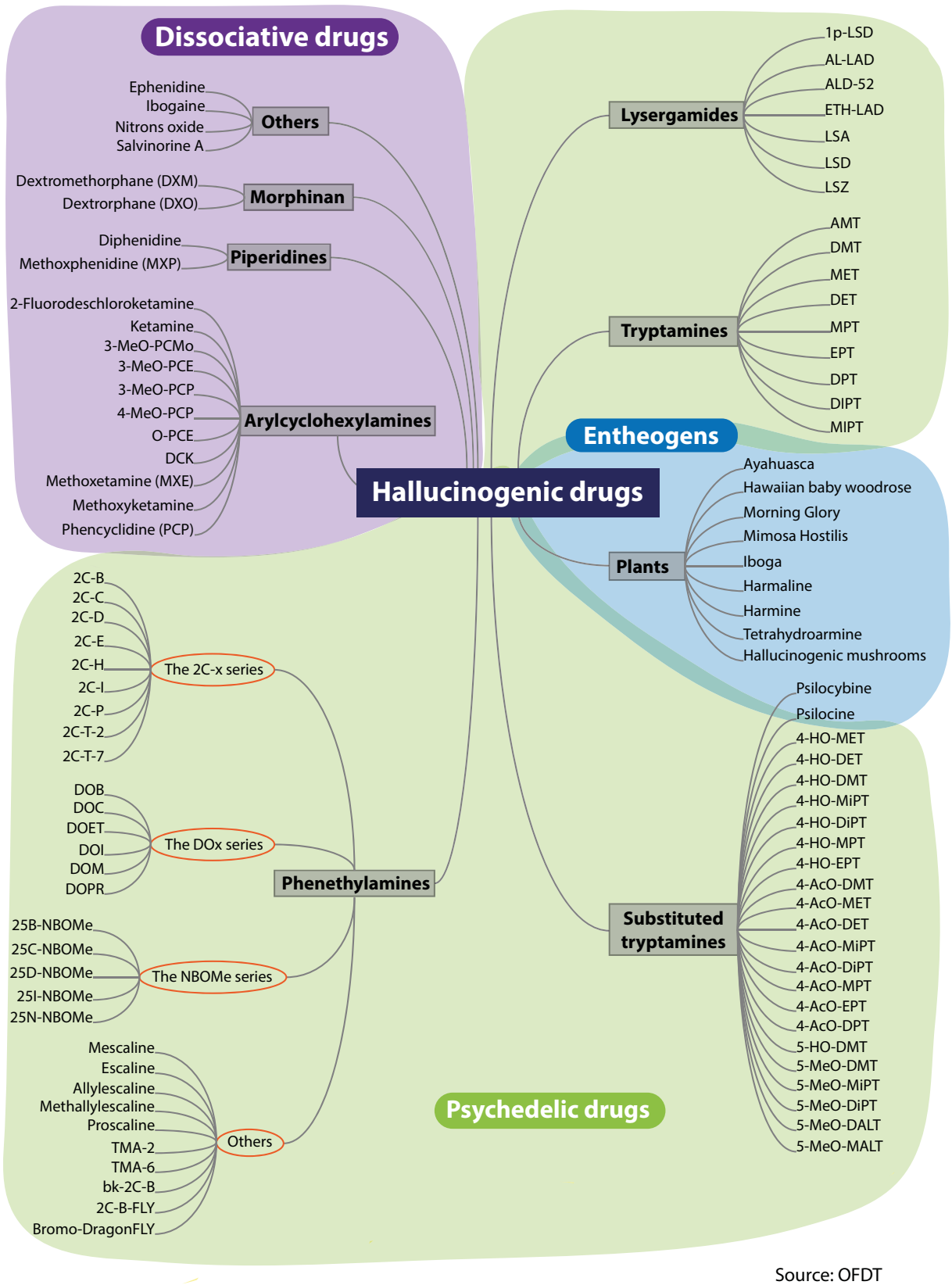
2016: COMPETITION WITH OTHER COMPOUNDS

While the visibility of these substances continued to level off in 2016, they continued to be mentioned in drug user testimonies on the festive scene (especially in South-western, Eastern and North-eastern France, according to TREND sites in Bordeaux, Metz and Lille).

According to a TREND observer in Lille, "the LSD scam" in 2015 practically created a "crisis of confidence" with regard to this drug. In response, in the regions where the 25*x*-NBOMe appeared to be more noticeable they were starting to be sold under their real name.

In the short term, there is no evidence that voluntary use is developing except among the e-psychonauts and some drug users of the alternative festive scene. The deliberate search for these NPS has little visibility, in contrast to stimulant NPS in the cathinones class, such as 4-MEC and 3-MMC (Debruyne *et al.*, 2010; Fournier *et al.*, 2010; Lahaie and Cadet-Taïrou, 2010). User ambiguity with regard to 25*x*-NBOMe, which characterised the initial diffusion of these compounds, seems to be even stronger currently. Both rejected and viewed with suspicion, due to their potency, by the majority of recreational psychotropic substance users, it is the subject of experimentation by other users for this very reason, when the opportunity arises. The difference compared to the situation in 2013 is that more people are now aware of the existence of this compound. They can choose to try the substance with full background knowledge (thus probably limiting unintentional use). Nonetheless, in 2016, the market appeared to follow the predominant trend of rejection and mistrust among users. It focused on longer-standing substances, such as DMT (a natural substance), DOC or 2C-B, which have a more positive and reassuring image among users.

Figure 1 - Graphical representation of the different types of existing hallucinogens (non-exhaustive list)

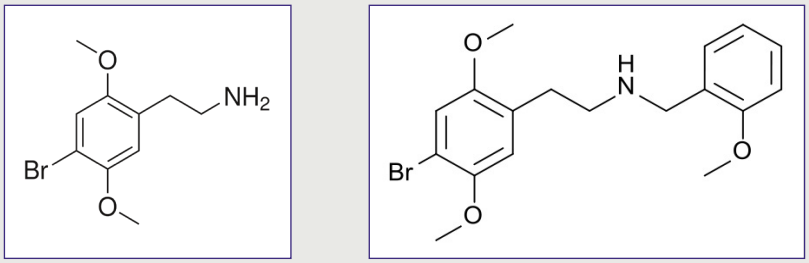


Source: OFDT

For a visual illustration of the emergence of 25*x*-NBOMe, refer to the annual index of NPS identified in France, animated version: http://www.ofdt.fr/produits-et-addictions/de-z/nouveaux-produits-de-synthese/animation-liste-nps/
or Excel format: https://www.ofdt.fr/download_file/view/2217/164/

PHARMACOLOGY

Originally manufactured during research into serotonin receptors, 25*x*-NBOMe belongs to the large class of phenethylamines and is very similar to the 2C-*x* (2,5-dimethoxyphenetylamines) group, a molecular series known in France since the arrival of the techno movement, in the 1990s, belonging to the same chemical class. It is characterised by the substitution of a methoxybenzoyl group on the amine of a 2C-*x*. Hence, 25I-NBOMe is the N-2-methoxybenzoyl derivative of 2C-I, 25B-NBOMe that of 2C-B, and 25C-NBOMe that of 2C-C, etc.



Chemical structure of 2C-B and its derivative 25B-NBOMe (Tang et al., 2014)

2C-*x*, like 25*x*-NBOMe, is a serotonin receptor agonist (5-HT). However, in vitro studies have shown that adding a methoxybenzoyl group to dimethoxyphenetylamines could lead to a 7 to 300-fold increase in the affinity for the 5-HT2A receptor subtype (Braden *et al.*, 2006). 25x-NBOMe is therefore a potentially more powerful molecule than 2C-*x*, and the studies conducted by Halberstadt and Geyer (Halberstadt and Geyer, 2014) in mice, indeed, confirm an increase in the effects. These molecules are also more powerful agonists of the other two 5-HT_{2B} and 5-HT_{2C} serotonin receptor subtypes, but also of α1 adrenergic receptors, $D_{1-3,}$ dopamine receptors, H1 histamine receptors and monoamine transporters. Due to its greater affinity for α1 receptors, 25*x*-NBOMe has more stimulant properties than LSD (Rickli *et al.*, 2015). This is evidenced by more potent effects, but also a greater overdose risk.

25*x*-NBOMe is metabolised by cytochromes P450 2C9 and 3A4. It mainly undergoes O-demethylation, O,O-bis-demethylation and hydroxylation in the first stages of metabolism, followed by the formation of conjugates by glucuronidation or sulfation. In vitro studies thus made it possible to identify 37 different metabolites in the first stages of metabolism (Caspar *et al.*, 2015). Due to the small quantities of 25*x*-NBOMe generally taken, together with the numerous transformations, it is difficult to detect these molecules or their metabolites in urine (Richeval *et al.*, 2017).

LEGAL STATUS IN FRANCE AND THROUGHOUT THE WORLD

In January 2014, the EMCDDA published an overview of the situation of the health and social consequences arising from the presence of 25I-NBOMe in European Union (EU) member states (EMCDDA and Europol, 2014). Its recommendation to conduct a risk assessment on this molecule was followed by the Council of the EU which, in September 2014, first took the resolution to submit the molecules of this group to control measures[10] (Council of the European Union, 2014).

At the same time, the Expert Committee on Drug Dependence, convened by the World Health Organization (WHO), conducted a worldwide risk assessment on 25B, C and I-NBOMe[11] in the summer of 2014 (WHO, 2015). The committee notably concluded that the clandestine production and absence of therapeutic use of these compounds were elements in favour of a worldwide control. This was therefore undertaken, in March 2015, by the Commission on Narcotic Drugs, listing these substances in Table 1 of the 1971 Convention on Psychotropic Substances (Commission on Narcotic Drugs, 2015).

In September 2015, in compliance with European law, France applied the decision taken by the Council of the EU and banned 25I-NBOMe on its territory[12]. On 6 November 2015, it took steps to introduce the international controls, by issuing a decree controlling all NBOMe prohibited by the WHO, together with the majority of 25x-NBOMe molecules already identified in Europe. Moreover, it extended these bans to other possible forms, via a generic definition of their chemical class[13].

10. Further to a procedural violation, this ban was annulled in terms of the form (case C-595/14), but not the content of the ban itself, which remained valid, to be voted on again in October 2015.
11. The assessment documents on each molecule are available via the following link: http://www.who.int/medicines/areas/quality_safety/36thecddmeet/en/index4.html
12. Decree of 24 September 2015 modifying the decree of 22 February 1990 laying down the list of substances classed as narcotics. NOR AFSP1522761A.
13. Decree of 6 November 2015 modifying the decree of 22 February 1990 laying down the list of substances classed as narcotics. NOR AFSP1526800A.

ROLE AND DIFFUSION OF 25X-NBOME IN THE DRUG MARKET

At European level, eight newly identified compounds strictly correspond to the 25*x*-NBOMe[14] family, and another twelve are variants (e.g.: 25B-N(BOMe)2[15], 25I-NBF[16]). In France, five versions (B, C, D, H, I) and two variants have been identified.

25*x*-NBOMe, SOME OF THE MOST VISIBLE NPS AT NATIONAL LEVEL

As part of the I-TREND project, a methodology was developed to identify the most widely circulating NPS on a national scale[17]. In 2013 and 2014, 25I-NBOME was estimated as being the most widely diffused.

USER INTEREST IN 25*x*-NBOMe

Great appeal in France

According to the findings of the I-TREND project (including four other European countries: Czech Republic, United Kingdom, the Netherlands and Poland), the NPS with psychedelic effects, such as 25*x*-NBOMe, or with dissociative effects[18], appear to have a greater presence in France than in the other countries involved in the project.

An online survey carried out in France among NPS users, from 20 June to 29 October 2014, was able to confirm the findings concerning users of these substances (Cadet-Taïrou, 2016). It supports the data obtained from the online forums, illustrating common points and differences between France and I-TREND European partners. Only the Netherlands and France have a noteworthy level of interest for 25*x*-NBOMe compared to the other NPS mentioned.

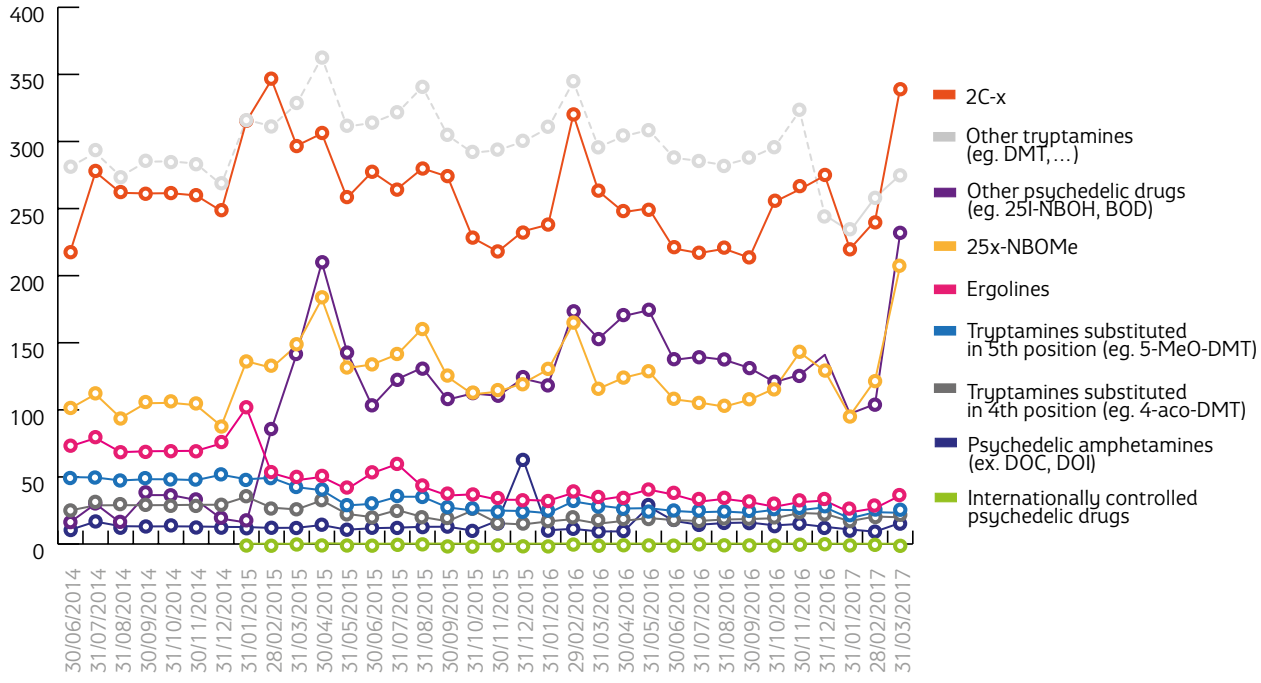
14. Versions B, C, D, E, G, H, I, N.
15. 2-(4-bromo-2,5-dimethoxyphenyl)-N,N-bis(2-methoxybenzyl)ethanamine.
16. 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-fluorophenyl)methyl]ethanamine.
17. The European project Internet-Tool for Research in Europe on New Drugs took place between 2013 and 2016, coordinated by the OFDT. It brought together 5 countries: France, the Czech Republic, the United Kingdom, the Netherlands and Poland. I-TREND aimed to deploy a rational online observation system, similar to the system normally used by the OFDT as part of its activities. Its operation led to the selection of the most widely diffused NPS in each country, requiring extensive documentation, based on the information sources normally used and specially developed within the scope of the project. See the website http://www.i-trend.eu/ for a detailed presentation of this project, a summary and all of the final reports (in English).
18. A feeling of dissociation between physical senses and the mind which can go as far as out-of-body experiences.

A specific target audience

Data from French-speaking forums and the online survey show that 25*x*-NBOMe have gained a foothold among sub-groups of internet users and/or users familiar with "psychonautism". A comparison of forum activity shows that most views[19] on psychedelics, the main family associated with 25*x*-NBOMe, are by users with a culture associated with psychonautism. This family comprises numerous new daily views, ranking it after the two most widely consulted families: synthetic cannabinoids and cathinones (less than 400 *vs.* 600 to 800 per day). Among psychedelics, 25*x*-NBOMe constitute a relatively clearly defined group.

The online survey gives rise to a very similar result, showing that the respondents (N=358) prefer hallucinogens and psychedelic substances (Cadet-Taïrou, 2016). 25*x*-NBOMe, owing to their effects, meet their expectations in terms of use (Martinez, 2016). Among the respondents identified with certainty as last-year NPS users, 66, i.e. 18%, named a compound in the NBOMe family as a NPS used over this period[20]. The most recent NPS was one of the 25*x*-NBOMe for 19 individuals among the 265 users capable of naming the substance. This number may appear to be low; however, given the diverse responses, this group of compound ranked third among those most frequently named by users. 25I-NBOMe ranked sixth out of the 70 compounds described as the most recent NPS used.

Graph 1 - Changes in the average number of new daily views of online discussions relating to substances with psychedelic effects and classed by sub-group



Source: OFDT, French-speaking forums

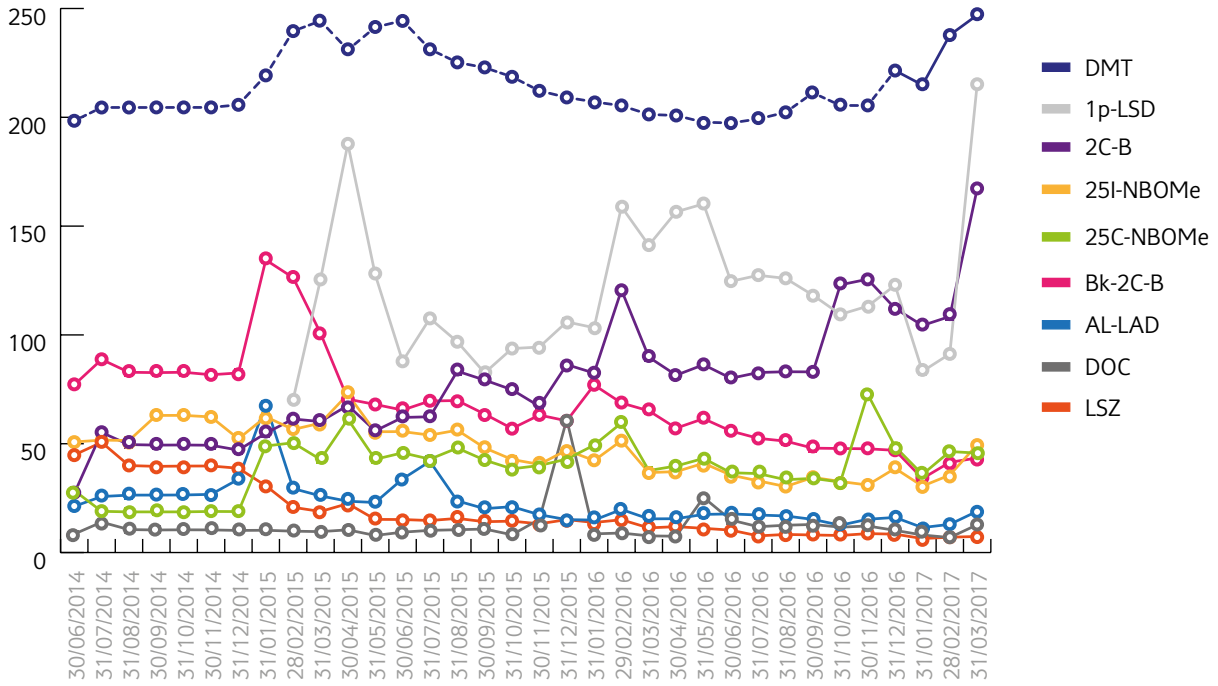
Note: The grey line indicating «other tryptamines» is broken when estimated and not calculated in the same way as for the other substances.

19. The number of views indicates the number of times the discussion web page has been opened by a user to be read. The number of views is not equivalent to the number of viewers, as a person may have visited the discussion thread several times a day.
20. The list of reported compounds was not exhaustive, as it was limited to 10.

Unequal and lower popularity compared to other psychedelic NPS

Among the twenty or so NBOMe type compounds or similar substances, listed at the European level (NBF, 30C-NBOMe, etc.), two substances, 25I-NBOMe and 25C-NBOMe were cited in particular. They have a very similar number of views on online forums, which are the highest of the NBOMe class. This is confirmed by the online survey: users are only aware of or limit themselves to a small number of compounds, and interest varies considerably from one to another. However, 25-I and 25-C have had a very stable audience over time.

Graph 2 - Changes in the average number of new daily views of online discussions relating to psychedelic molecules, among those most frequently accessed



Source: OFDT, French-speaking forums
Note: The blue line indicating «DMT» is broken when estimated and not calculated in the same way as for the other substances.

Several information sources (TREND, I-TREND online survey and forums) show that three classes of psychedelic substances, 2C-*x*, atypical psychedelic compounds and tryptamines, attract greater interest from users compared to 25*x*-NBOMe.

Like 25*x*-NBOMe, these three classes are driven by key compounds (see Figure 1, p. 7). The largest class of psychedelic substances, 2C-*x*, is mainly represented by 2C-B. The "atypical psychedelics" class brings together diverse compounds (lysergamides and other phenethylamines), notably 1p-LSD[21] which acts as a prodrug[22] of LSD (Brandt *et al.*, 2016). The tryptamines class (AMT, DMT, etc.) is mainly driven by DMT.

21. N,N-diethyl-7-methyl-4-propanoyl-6,6a,8,9-tetrahydroindolo[4,3-fg]quinoline-9-carboxamide.
22. A prodrug is a molecule taken in an inactive pharmacological form which is metabolised into a pharmacologically active molecule.

TRAFFICKING: FROM VISIBILITY AT THE BOUNDARIES TO MICRO-TRAFFICKING

The information provided by the customs services, police and *Gendarmerie* confirms the above data. It also states that DOC and 2C-*x* type substances are the most frequently intercepted psychedelic compounds, and that the 25*x*-NBOMe class, usually ranking in fourth place, is mainly represented by 25I and 25C.

Prior to 2014, visibility in cross-border circulation

These substances were first identified in France on 27 July 2012 at Roissy-Charles de Gaulle airport, in a package that was shipped from China. It contained 2 grams of 25I-NBOMe in the form of a white powder. After this seizure, the Customs Joint Laboratories Department (SCL) identified another four seizures which all concerned 25I-NBOMe. In total, in 2013, out of 1,153 NPS seizures by all departments combined, 12 concerned 25*x*-NBOMe[23] (i.e. 1.04%).

Since 2014, a swing towards micro-trafficking

Out of the 1,200 seizures involving NPS[24] in 2014, 15 concerned 25*x*-NBOMe (i.e. 1.2%). In 2015, these represented an equivalent proportion (11 out of 865 seizures) and were fewer in number in 2016 (5 out of 1,211 seizures, i.e. 0.4%). The variety of 25*x*-NBOMe molecules examined by the law enforcement agencies has decreased considerably since 2014.

Another major change resides in the fact that observation is no longer exclusively within the remit of customs. Compared to 2013, the police and *Gendarmerie* services, which focus more on the national territory than the point of entry into the country, seized greater quantities of 25*x*-NBOMe in 2015. These compounds are less visible in postal freight cross-border circulation, but their presence is, paradoxically, greater during manual body searches. This change suggests that, despite their reduced presence in international flows, 25x-NBOMe have a genuine, albeit small presence in micro-trafficking networks. This, moreover, varies considerably according to the cities, with a more marked presence in the Bordeaux, Lille and Metz recreational scenes. Law enforcement agents in the Lille region thus reported mainly cathinones and 25*x*-NBOMe in seizures, rather than the cathinones/synthetic cannabinoids combination normally observed in this territory (Lancial and Lose, 2014a).

23. 3 x 25B-NBOMe, 1 x 25C-NBOMe, 8 x 25I-NBOMe.
24. After excluding plants such as khat, so that only synthetic substances are taken into account. The total number of seizures of "new psychoactive substances" in France reached 1,360 in 2014.

SALES AND PURCHASING PATTERNS

MORE REAL LIFE SALES THAN INTERNET SALES

The results of the online survey among NPS users illustrate a constant parameter in the field of drugs, corresponding to the importance of social environment in drug availability. The Internet is the supply source; however, overall, one in two NPS users obtained their most recently used NPS via their social circles. Hence, 11 of the 19 individuals[25], for whom a 25*x*-NBOMe was the last substance used, obtained it from an intermediate party, free of charge or purchased from a friend or a drug dealer. In the ethnographic interviews carried out by TREND, or in SINTES collections, the source of the purchase also tends to be a drug dealer rather than a website.

CHANGES IN THE FORMS AVAILABLE ON THE MARKET

In 2013, the initial findings obtained via SINTES collections showed that 25x-NBOMe were sold in the form of a coloured liquid, sometimes packaged as a nasal spray. This presentation, atypical in the field of drugs, is a marketing innovation by online drug dealers. This has been observed at the Bordeaux and Lille TREND sites, but has not been confirmed by chemical analysis of the substance sold. The liquid form was practically the only form available to users at the time.

In 2016, the liquid form was still observed, but usually by the customs services, in postal freight. As trafficking has swung to micro-trafficking, the blotter form has become more common in customs and police seizures (20 out of 31 cases). The predominance of this form illustrates the way in which dealer sales are adapting the marketing approach. In 2015 and 2016, TREND and SINTES data thus indicated the practical disappearance of the liquid form "on the ground", in favour of the blotter form.

Seized blotters / © Service commun des laboratoires des Douanes

25. These data on a very small sample size are provided as an illustration rather than for statistical purposes.

At the same time, perhaps owing to this new form, sales of 25x-NBOMe appeared to extend from the exclusive alternative recreational setting to the general electronic music recreational scene. Hence, in 2016, a relatively large quantity of blotters containing 25x-NBOMe was seized from an individual in a Paris nightclub.

TRANSPARENCY AND NORMALISATION OF NAMES

In 2013 to 2016, sales practices for 25*x*-NBOMe started to become more normalised, starting with the use of invented names, fraudulent names, via names suggesting the synthetic nature of the substance, and ultimately resulting in the use of its own name. In face-to-face sales, users may be even more dependent on the information provided by drug dealers than on the Internet. The way in which the dealer presents the substance is important, as the name provides information on the authenticity of the purchase. Ambiguous names are more informative than using the name LSD, in the sense that users are aware that it is a different substance to LSD.

On one hand, some dealers chose not to use the real name of the compound because they feared that users would not purchase it under its real name, either because they would not know how to use it, or because it may not have a good image. This technique caused the recent "confidence crisis" with regard to LSD (Milhet *et al.*, 2017).

On the other hand, dealers are selling 25*x*-NBOMe under their names, thereby taking on the role of initiators. They select a compound or indicate dosages according to the individual's weight and former experiences (Bordeaux 2015). Introducing compounds under their real names tends to show that suppliers are, more than ever before, familiar with the nature of the substances sold. This does not necessarily indicate greater acceptance among users, but rather that it may be becoming normalised among sub-groups more inclined to experiment with these substances.

It was only in late 2015-early 2016 that 25*x*-NBOMe began to be referred to more frequently by its own name on a local level. It is now sometimes shortened and simplified to 25x, or "NBOMe". In early 2016, two new sample collections took place according to this pattern, in the same city in the south of France. One evidenced up to three different 25*x*-NBOMe molecules on the same blotter, and the other an unknown derivative of this class.

PATTERNS OF USE AND REPRESENTATIONS

When these compounds emerged, numerous rumours concerning their patterns of use circulated on forums and in a real-life setting. In particular, it was claimed that these substances were inactive when taken orally, unlike LSD. Although the presence of a methoxybenzoyl group on the molecule suggests a major "hepatic first-pass" effect[26] (Chao *et al.*, 2010) transforming 25x-NBOMe into inactive metabolites, no pharmacokinetic data currently exist concerning the inactivated constituent. Moreover, it has been established that an active constituent still remains after oral administration. Cases of non-fatal overdose have been reported following oral intake of powder, capsules (Hill *et al.*, 2013) or liquid (WHO, 2014). Sublingual, buccal, oral and nasal routes of administration have, moreover, been described by users (Lawn *et al.*, 2014).

26. The "hepatic first-pass" effect is a biological mechanism. Following oral intake, the molecule passes through the liver, where chemical transformation takes place. This is known as metabolism, which changes the ingested molecules into other more or less active molecules.

Nonetheless, this idea, widespread during the early diffusion of 25*x*-NBOMe, particularly in the liquid form, has become deeply entrenched in behaviours. When sales gained a foothold on the real market in 2014-2016, with the blotter forms, the most scrupulous drug dealers sometimes advised their clients to take the substance via the sublingual route, which involved leaving the blotter under the tongue to allow the active substance to pass through the mucous membranes[27]. The online survey and ethnographic data obtained via TREND, SINTES and I-TREND show that users fully adhered to this pattern of use.

Ultimately, some users concluded that, in case of doubt as to the true nature of a substance sold as LSD, it would simply need to be swallowed (to inhibit the effects if the substance indeed proved to be 25*x*-NBOMe). Based on current knowledge, it could be dangerous for users to adopt this idea as a harm reduction measure. Without a chemical analysis, fragmented intake would be the only way to limit the potential risk of intoxication.

27. The substance then passes directly into the blood circulation, avoiding the hepatic first-pass effect.

EFFECTS AND INTOXICATION CASES

There is a vast amount of literature, both in France and abroad, on the toxicity and adverse effects of 25x-NBOMe, based on clinical cases (Bodeau *et al.*, 2017; Boucher *et al.*, 2015; EMCDDA *et al.*, 2014; Hill *et al.*, 2013; Lawn *et al.*, 2014; Tang *et al.*, 2014; WHO, 2015; Wood *et al.*, 2015). However, few user testimonies on the effects occurring below the toxicity levels are available.

EXPECTED EFFECTS

The expected effects are similar to those arising from conventional serotonergic hallucinogens, such as psilocybin or LSD, with more or less potent visual and audible hallucinations. Depending on the pattern of use -oral, sublingual, buccal or nasal route- the effects appear after 20 minutes to 1 hour and can last 3 to 13 hours (Lawn *et al.*, 2014). In some cases, these can persist for several days.

In the online survey, the most common reasons (sometimes multiple) given by users having recently taken 25*x*-NBOMe were based on the very nature of psychonautism: the desire to alter perceptions (17 responses), or the desire to use the substance to improve sociability (11 individuals). To a lesser extent, the responses then focused on a desire to "get stoned", to "have energy" or to "stimulate intellectual activity" (6 or 5 responses each).

ADVERSE EFFECTS

The adverse effects reported comprise psychiatric effects (delirium, agitation, aggressiveness, violence, paranoia, confusion) and physiological effects (vomiting, nausea, tachycardia, arrhythmias, high blood pressure, stroke, tachypnoea, excessive perspiration, hyperthermia, metabolic acidosis, rhabdomyolysis, kidney failure, multiple organ failure) (Wood *et al.*, 2015).

These various symptoms were reported following management by the health services (Ameline *et al.*, 2017; Bersani *et al.*, 2014; Boucher *et al.*, 2015; Hill *et al.*, 2013; Tang *et al.*, 2014) and also during the collection of substances carried out and reported by the OFDT, after unpleasant experiences by users who did not seek medical assistance. This is a frequent occurrence, particularly with psychedelic substances because, despite intoxication, users only tend to approach professionals in the event of a life-threatening emergency. Hence, in the online survey, 12 out of 19 individuals experienced unpleasant effects without seeking treatment. Seven individuals experienced negative psychological effects and 8 physical effects[28].

28. Nine of the 21 proposed types of adverse effects were mentioned. These primarily concerned heightened anxiety or an episode of paranoia (5 responses), then, to an almost equal extent, unpleasant hallucinations, extreme fatigue or stimulation, causing insomnia or a feeling of exhaustion, cramps, jaw-clenching (2 responses for each item).

In addition, craving, seizures, motor difficulties and hot flushes were also mentioned. According to the SINTES collections, one individual who took 25H-NBOMe sold under the name "Vortex" claimed to have experienced a loss of sense of time, stomach pain with nausea and vomiting, together with profuse diarrhoea, one hour after intake.

All of the TREND sites point out that the exceptionally long duration of the effects, sometimes ten or so hours, and the difficult "coming down" are major factors in users distancing themselves from these compounds. According to the Bordeaux site, "the duration of the effect of one drop is approximately 6 hours, with a high estimated at one hour and body load[29] lasting more than 24 hours" (Lazès-Charmetant and Delile, 2014a). The impossibility for an individual to stop the ongoing experimentation is likely to generate all of the above-mentioned psychological adverse effects. These may be intensified if the individual expected a shorter duration or lower intensity of effects, which would have corresponded to LSD.

These adverse effects, despite not automatically resulting in treatment, were sufficiently important to prompt self-support associations, in 2013, to create a flyer on the risks related to NBOMe[30]. Use of these substances, like many other NPS, without real knowledge of their identity is perceived by harm reduction workers in the recreational setting as a trigger for problematic experiences. Users thus appear to describe this type of experience as bad trips which are particularly difficult to endure.

The rapid development of tolerance further to repeated intake within a week has also been reported.

HEALTH SIGNALS REPORTED TO THE MONITORING SCHEMES

On a European level, several health alerts concerning 25I-NBOMe[31] were reported in 2013.

The adverse health events recorded over the 2013-2014 period could be related to the new diffusion of these molecules, particularly in the recreational setting.

Users are then particularly exposed to accidents as they may be unaware of the nature of the consumed substance or insufficiently informed of the dosage strengths and duration of effects. The absence of health cases after this period may be due to either a major reduction in the availability of the substance, or adaptation of user and dealer behaviours to this new supply. The switch to the blotter form in particular has limited the doses actually ingested by users compared to the liquid form.

29. Strictly speaking, body load is an unpleasant and diffuse physical sensation resulting from intake of a psychoactive substance. However, body load is not necessarily exclusive, and may be accompanied by or interspersed with pleasant sensations. In a broader sense, body load is sometimes understood as being all of the adverse effects liable to be experienced after drug use, regardless of the length of time between actually taking the substance and onset of these effects.
30. https://web.archive.org/web/20150902125957/http://www.technoplus.org/t,1/2736/25i-nbome-/-25c-nbome and http://technoplus.org/wp-content/uploads/sites/2/2016/12/Flyer_2C-MXE-25i_2016web.pdf Accessed on 18/10/2017
31. United Kingdom, 7 unrelated cases of acute intoxication; Belgium, 3 cases of acute intoxication following the purchase of blotters containing 25I-NBOMe.

All of the signals are reported by several different channels and may sometimes overlap.

- Two events concerning the analysis of biological samples containing NBOMe were reported by the Grenoble and Lyon CEIPs, one in late 2013 – early 2014[32], and the other in 2014 (Boucher *et al.*, 2015).

- In early 2014, two cases of confinement to a psychiatric institution supposedly resulting from use of NBOMe were also reported via forums.

- Four different signals were reported in a summary drawn up by the Île-de France Regional Health Agency[33] in 2012-2014, including two cases possibly already reported.

- The ANSM, during its risk assessment on 25*x*-NBOMe, in addition to the above reports, communicated four spontaneous reports observing the use of these substances, without analytical confirmation[34].

- In 2016, two cases of acute intoxication in the gay community resulted in admission to the emergency department (Ameline *et al.*, 2017).

Definition of a health signal

Health signals are defined in this instance as the collection of sufficient information to establish that an individual has received health care, without it being systematically possible to obtain and compile the clinical data related to treatment.

32. Grenoble CEIP, report communicated by the ANSM, indirect death of an individual. This means that the person took the substance, but died as a result of another event (e.g.: pedestrian knocked over by a vehicle, drowning, etc.).
33. http://docplayer.fr/27770697-Synthese-synthese-des-reunions-veille-et-alerte-psychotropes-et-stupefiants.html Accessed on 18/10/2017
34. http://ansm.sante.fr/var/ansm_site/storage/original/application/65da663e2c365f71aa2ac21741f47603.pdf Accessed on 18/10/2017

CONCLUSION: COMPOUNDS THAT SYMBOLISE A DIFFUSION PATTERN FOR NEW HALLUCINOGENIC SUBSTANCES

The way in which 25x-NBOMe emerged in the general drug landscape in France very closely resembles the emergence of methoxetamine (Lahaie and Martinez, 2011). These NPS are similar to ketamine and LSD, for methoxetamine and 25*x*-NBOMe, respectively. Now, ketamine and LSD are two drugs particularly sought after in the alternative recreational setting in France; however, their availability is often unreliable (Gandilhon *et al.*, 2014; Milhet *et al.*, 2017; Reynaud-Maurupt *et al.*, 2007).

The pharmacological similarity of these substances encourages the use of these NPS as substitutes among drug dealers. As suggested by the comparison of data originating from the TREND scheme and the I-TREND European project, the emergence of 25*x*-NBOMe in the recreational settings in 2013, along with methoxetamine in 2011, was generated by dealers rather than the users themselves. Like the latter, the diffusion of 25*x*-NBOMe was a sudden occurrence, before it disappeared from several observation sources (ANSM, SINTES, etc.).

The emergence followed by the apparent practical disappearance of these compounds also illustrate the way in which the market reacts and adapts in the mid-term to the presence of a new substance in dealing circuits, in addition to NPS use as substitutes for conventional drug supply (Winstock and Wilkins, 2011). These changes concern a small fraction of the drug market, usually in the recreational setting, but with a higher prevalence of psychotropic substance use compared to the general population.

The cycle begins with an offensive diffusion phase driven by real-life supply. This stage is characterised by situations with higher levels of use, resulting in health incidents. NPS diffusion is highly visible during this period, particularly due to these events. In the next phase, a number of strategies are introduced to regulate the presence of these new substances, both by drug dealers and users. This is lastly followed by a phase in which adaptation of the market makes it harder to evidence the circulation of these compounds. While the prevailing attitude is still a certain degree of suspicion, a larger proportion of users potentially interested in these substances is now aware of their existence. Other than e-psychonauts, more consumers frequenting the recreational scene may take an interest in these substances. Dealers may continue to adapt this new supply to user habits, particularly by reducing the dosage strengths. In all cases, if NBOMe use becomes established, this can only be observed over the longer term. Since 25*x*-NBOMe is used as an "adjustment variable" for the availability of LSD, its visibility could continue to be determined by the latter (Bodeau *et al.*, 2017). This substitution of one molecule for another can only, however, be evidenced if analyses of the substances are able to verify the exact content of the substances sold.

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Within the vast category of new psychoactive substances, 25*x*-NBOMe or NBOMe represents a group of compounds in the phenethylamine family, which mainly has a hallucinogenic and psychedelic effect in particular.

These compounds, which are sometimes sold and used instead of LSD, have emerged on the French market over the past five years.

Based on the different activities carried out by the TREND-SINTES schemes and the I-TREND European project, this summary attempts to explain how 25x-NBOMe were able to attract obvious interest among certain users. It describes the way in which these substances have established a presence in France, according to a relatively symbolic diffusion pattern for new hallucinogenic substances. This analysis also focuses on the prospects for changes and the limits of their presence on French territory. Lastly, it presents and describes their inherent challenges and problems, particularly in relation to health.

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